FDA Executive Summary

Prepared for the
September 12, 2013 meeting of the
Circulatory System Devices Panel

Classification of the Membrane Lung for Long-term Pulmonary Support [Extracorporeal Membrane Oxygenator – ECMO (21 CFR 868.5610)]

TABLE of CONTENTS

Overview **3**
Device/Circuit Description **6**
Regulatory/Review History and Indications for Use for 21 CFR 868.5610 .... **8**
Classification History for 21 CFR 868.5610 .... **11**
Discussion of Risks to Health **18**
Summary of Evidence **21**
Medical Device Report (MDR) Analysis and Recalls 21
Literature Review 29
Clinical Evidence 35
Summary of FDA Recommendation **48**
Mitigations for Identified Risks/Overview of Proposed Special Controls 48
Regulation 51
Current 51
Proposed 51
APPENDIX A **53**
References cited in Literature Search 53
Appendix B **56**
Publications Included in Literature Review 56

Overview

On September 12, 2013, the Food and Drug Administration (FDA) will convene the Circulatory System Devices Advisory Committee to discuss the classification of the membrane lung for long-term pulmonary support [extracorporeal membrane oxygenation] (21 CFR 868.5610).

21 CFR 868.5610, membrane lung for long-term pulmonary support refers to the oxygenator component of an extracorporeal circuit for long-term procedures, commonly referred to as ECMO. However, many components make up the extracorporeal circuit for ECMO use. Currently, there are no regulations defining the other extracorporeal circuit components that comprise an ECMO circuit (long-term durations of use). Additionally, the membrane lung for long-term pulmonary support is currently defined very narrowly in terms of both intended use (gas exchange only), and technology (membrane oxygenator only). As such, a broader definition and identification is being proposed and a realignment of the classification regulation to include 1) all of the circuit components/accessories needed for long-term extracorporeal support, and 2) flexibility for current technology, to provide an efficient approach to regulate an entire system that provides and/or participates in long-term extracorporeal support.

The membrane lung for long-term pulmonary support devices, referred to as extracorporeal membrane oxygenation, hereinafter referred to as ECMO, are one of the remaining preamendment Class III medical devices currently cleared for marketing through the premarket notification [510(k)] pathway. FDA has proposed a revised definition/identification for ECMO for inclusion within the Cardiovascular classification regulations, as well as reclassification from Class III to Class II (Special Controls) for a specific subset of patients and conditions where ECMO therapy has demonstrated to be standard of care[a] .

In summary, the following changes are being recommended for the current classification regulation to ensure more appropriate identification and alignment of the products as they are used clinically.

1) Renaming the title of the classification regulation:
    a. FROM: *Membrane Lung for Long-Term Pulmonary Support*
    b. TO: *Extracorporeal Circuit and Accessories for Long-Term Pulmonary/Cardiopulmonary Support*.

2) Redefining and changing the definition/identification of the regulation number from Anesthesiology devices to fall within Cardiovascular devices:
    a. FROM: *Identification: A membrane lung for long-term pulmonary support is a device used to provide to a patient extracorporeal blood oxygenation for longer than 24 hours.*

[a] Federal Register, January 8, 2013, Vol. 78, No. 5, p. 1158

b. TO: *Identification: An extracorporeal circuit and accessories for long-term pulmonary/cardiopulmonary support (>6 hours) is a system of devices that provides assisted extracorporeal circulation and physiologic gas exchange of the patient's blood where an acute (reversible) condition prevents the patient's own body from providing the physiologic gas exchange needed to sustain life in conditions where imminent death is threatened by respiratory (e.g., meconium aspiration, congenital diaphragmatic hernia, pulmonary hypertension) in neonates and infants, or cardiorespiratory failure (resulting in the inability to separate from cardiopulmonary bypass following cardiac surgery) in all pediatric patients. An acute reversible or treatable cause of respiratory or cardiorespiratory failure should be evident, and the subject should demonstrate unresponsiveness to maximum medical and/or ventilation therapy. The main components of the system include the console (hardware), software and disposables, including but not limited to, an oxygenator, blood pump, heat exchanger, cannulae, tubing, filters, and other accessories (e.g., monitors, detectors, sensors, connectors).**

3) Defining "long-term" support as extracorporeal support >6 hours (i.e., anything beyond typical cardiopulmonary bypass support [≤6 hours]) instead of >24 hours.

4) Recommending a classification of Class II (Special Controls) where imminent death is threatened by respiratory failure (e.g., meconium aspiration, congenital diaphragmatic hernia, pulmonary hypertension) in neonates and infants, or cardiorespiratory failure (resulting in the inability to separate from cardiopulmonary bypass following cardiac surgery) in pediatric patients.

**The specific wording for the proposed reclassification is clarified when compared to the proposed order (published January 8, 2013)*[a] *based on comments received from the public and industry to the January 8, 2013 proposed order, where specific conditions and patient populations to be included in the reclassification were not clear.*

The recommended reclassification from Class III to Class II is based on a systematic literature search and clinical review of the information/data available for ECMO therapy in the proposed patient population (see the Summary of Evidence section below), as well as the data available through the Extracorporeal Life Support Organization (ELSO) registry and other institutional experience.[b c] If the panel agrees with the Class II recommendation being proposed, then the panel will also be asked to discuss the adequacy of the special controls proposed by FDA to mitigate the risks to health.

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[b] Fleming, MD, Geoffrey M., et al., Pediatr Crit Care Med. 2009 Jul; 10(4): 439-44
[c] Cook, LN, Paediatr Respir Rev. 2004; 5 Suppl A:S329-37

Below is FDA's proposed regulatory classification strategy:

FDA Proposed Regulation and Classification for ECMO devices

21 CFR 870.4100 *Extracorporeal circuit and accessories for long-term pulmonary/cardiopulmonary support*:

(a) *Identification*. An extracorporeal circuit and accessories for long-term pulmonary/cardiopulmonary support (>6 hours) is a system of devices that provides assisted extracorporeal circulation and physiologic gas exchange of the patient's blood where an acute (reversible) condition prevents the patient's own body from providing the physiologic gas exchange needed to sustain life in conditions where imminent death is threatened by respiratory failure (e.g., meconium aspiration, congenital diaphragmatic hernia, pulmonary hypertension) in neonates and infants, or cardiorespiratory failure (resulting in the inability to separate from cardiopulmonary bypass following cardiac surgery) in all pediatric patients. An acute reversible or treatable cause of respiratory or cardiorespiratory failure should be evident, and the subject should demonstrate unresponsiveness to maximum medical and/or ventilation therapy. The main components of the system include, but are not limited to, the console (hardware), software and disposables, including but not limited to, an oxygenator, blood pump, heat exchanger, cannulae, tubing, filters, and other accessories (e.g., monitors, detectors, sensors, connectors).

(b) Class II (special controls).

As discussed in the Introduction & Regulatory Reference Sheet provided, the panel will need to consider the risks to health for the extracorporeal circuit and accessories for long-term pulmonary/cardiopulmonary support as a class, and determine whether the information available, which is subsequently discussed, fits the following criteria:

(i) The information represents valid scientific evidence (according to 21 CFR 860.7) that is adequate to demonstrate a reasonable assurance of product safety and effectiveness; and
(ii) Special controls can be appropriately established to mitigate the identified risks to health.

The Panel is tasked with discussing whether the risks to health for the extracorporeal circuit and accessories for long-term pulmonary/cardiopulmonary support have been appropriately identified. Further, the panel will be asked to discuss the available scientific evidence for the currently-marketed technologies, indications, and clinical use.

As defined in 21 CFR 860.7(d)(1), there is reasonable assurance that a device is safe when it can be determined, based upon valid scientific evidence, that the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risks. As defined in 21 CFR 860.7(e)(1), there is a reasonable assurance that a device is effective when it can be determined, based upon valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results.

If a recommendation of Class III is made, each device and accessory would be expected to provide an independent dataset to demonstrate a reasonable assurance of safety and effectiveness prior to marketing the device. The collection of such data translates into establishing an initial knowledge basis of safety and effectiveness information on which to rely. Class III devices, regulated through the PMA program, can be considered for reclassification at a later date once a valid scientific body of evidence has been collected to establish safety and effectiveness and special controls can be developed to mitigate risks.

If a recommendation of Class II is made, then it should be noted that it is the current body of evidence considered as part of this panel meeting that will be leveraged to support future substantially equivalent determinations through the 510(k) program. Special controls would be required to provide continual assurance through mitigating known risks that any new devices coming to market through the 510(k) program are "as safe and effective" as the predicate(s) (Refer to Section 513(i)(1)(A) of the FD&C Act).

FDA is holding this classification panel meeting to obtain comments and recommendations from the panel regarding whether ECMO as redefined by FDA should remain in Class III (subject to PMA) or be reclassified to Class II [subject to 510(k)]. The panel will be asked to provide input on the risks to health and benefits of ECMO including the membrane lung for long-term pulmonary support (868.5610) and other devices required in an extracorporeal circuit to perform ECMO therapy. The panel will also be asked to discuss the FDA's proposed regulatory classification strategy for ECMO devices. If the panel agrees with a Class II recommendation as proposed, the panel will also be asked to specifically discuss the appropriateness of the proposed special controls necessary to mitigate the identified risks to health.

FDA believes that there is sufficient safety and effectiveness information to recommend revising the name and identification of the regulation, and down classifying extracorporeal circuit and accessory devices for long-term pulmonary/cardiopulmonary support to Class II with appropriate special controls, in conjunction with general controls, in the identified infant/neonatal patient population.

Device/Circuit Description

A membrane lung for long-term pulmonary support (21 CFR 868.5610) is the name given to the oxygenator component of an extracorporeal circuit used during long-term procedures, commonly referred to as extracorporeal membrane oxygenation, or ECMO. An ECMO procedure, in current clinical practice, provides assisted extracorporeal circulation and physiologic gas exchange of the patient's blood during conditions consistent with acute reversible respiratory and/or cardiac failure, and comprises several devices (similar to a cardiopulmonary bypass circuit), including (but not limited to) an oxygenator, pump, cannula, heat exchanger, tubing, filters, various monitors/detectors and other accessories. ECMO is used as part of the standard of care (but not necessarily cleared or approved) for patients with acute reversible respiratory or cardiac failure, unresponsive to optimal ventilation and/or pharmacologic management. These criteria include a large range of respiratory failure indications/conditions including, but not limited to, meconium aspiration, congenital diaphragmatic hernia, and pulmonary hypertension in neonates and infants; and respiratory failure in adults (e.g., ARDS, COPD, failure to wean). ECMO is also being used (in all patient populations) for acute cardiac failure indications such as failure to wean and cardiogenic shock. An example of an ECMO circuit is shown below:

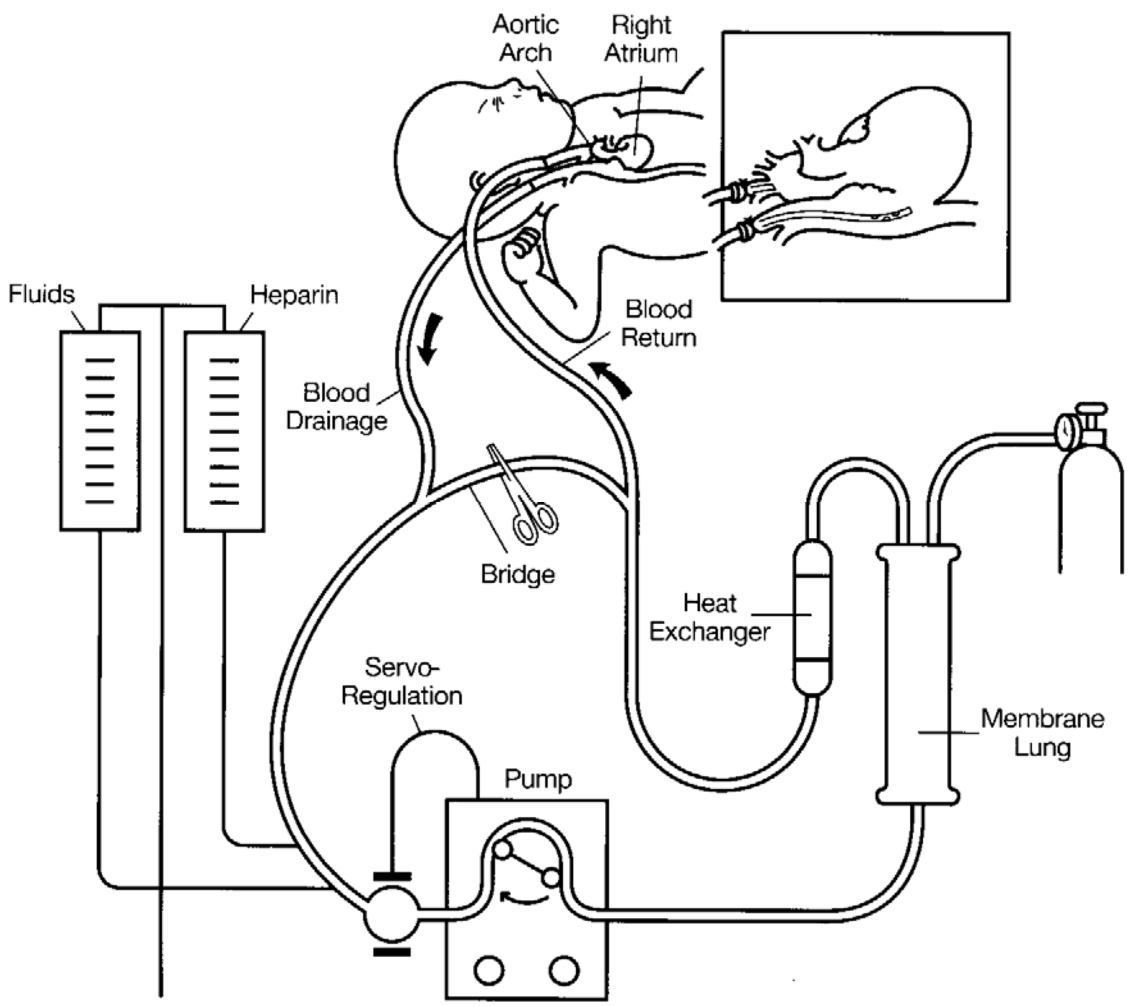


Figure 1: ECMO Circuit *(Source: Google Images)*

The regulation for membrane lung for long-term pulmonary support (21 CFR 868.5610) describes a specific gas exchange technology which includes the use of a membrane (e.g., silicone) that acts as a barrier between the blood flow and gas flows, but also has the ability to diffuse oxygen and carbon dioxide through the membrane based on pressure gradients – i.e., oxygen diffuses into the blood through the membrane because the pressure gradient for oxygen is higher on the gas side of the membrane, and carbon dioxide diffuses through the membrane from the blood because the pressure gradient for carbon dioxide is higher on the blood side of the membrane. This procedure enables the patient's circulating blood to continue physiologic gas exchange (using an extracorporeal circuit) when an acute (reversible) condition prevents their own body from providing the physiologic gas exchange needed to sustain life.

Depending on the patient and condition being treated, the circuit components and circuit configuration (e.g., arterio-venous, veno-venous) may vary. There are no classification regulations for the long-term use of any of the extracorporeal circuit components used for ECMO, except for the oxygenator component, *21 CFR 868.5610 Membrane lung for long-term pulmonary support*. There are regulations for each of the components used for ECMO, but currently they are defined only for short-term durations associated with cardiopulmonary bypass procedures (≤6 hours). Because the oxygenator cannot achieve the desired clinical therapy without the other circuit components, all of the device components used for ECMO are being considered in the scope of this reclassification strategy and proposed order that was published on January 8, 2013 for 21 CFR 868.5610 membrane lung for long-term pulmonary support.

Regulatory/Review History and Indications for Use for 21 CFR 868.5610

Clearance under the 21 CFR 868.5610 regulation:

The membrane lung for long-term pulmonary support devices, referred to as extracorporeal membrane oxygenation, hereinafter referred to as ECMO, are one of the remaining pre-amendment Class III medical devices currently cleared for marketing through the premarket notification [510(k)] pathway. This device type is a pre-amendment Class III device, meaning that this device type was marketed prior to the Medical Device Amendments of 1976 and was classified by the original classification panels as Class III, but for which FDA never established an effective date for the requirement for premarket approval (PMA). These devices were originally identified as a specific type of oxygenator (membrane technology vs. bubble technology, for example) designed to provide extracorporeal blood oxygenation for > 24 hours. The product code given to the membrane lung for long-term pulmonary support is **BYS** and there has been one (1) 510(k) submission for tubing (see immediately below) cleared under this classification regulation with this product code.

Tubing

K770720 (cleared August 4, 1977 under 21 CFR 868.5610 membrane lung for long-term pulmonary support, product code **BYS**, Class III).

Cleared Indications:

> The "William Harvey Extracorporeal Tubing Pack" was originally cleared as tubing for roller pumps. No specific indications for use statement was found since this was before CDRH was requesting Indications for Use forms.

K770720 was updated in Feb 1997 and included the following indications for use statement in the product labeling:

> *"This Bard Vascular Systems Extracorporeal Perfusion Pack is indicated for use during cardiopulmonary bypass procedures and constitutes the extracorporeal circuit in whole or part."*

Other ECMO Clearances

Many components make up the extracorporeal circuit for ECMO use. As such, a review history for devices that have been cleared with long-term/ECMO labeling include cardiopulmonary bypass devices and diagnostic intravascular catheters. Examples are provided immediately below:

Oxygenator

K863476 (cleared November 25, 1986 under 21 CFR 870.4350 Cardiopulmonary Bypass Oxygenator, product code DTZ, Class III [at the time][d])

Cleared Indications:

> *"SciMed Membrane Oxygenators are intended for use in an extracorporeal perfusion circuit for the oxygenation of and the removal of carbon dioxide from the blood."*

The manufacturer added the following statements to the labeling in K863476 for ECMO use:

> *"For prolonged bypass (> 6 hours), or other long-term applications such as ECMO, the following information must be considered:*
>
> - *ECMO applications require technical personnel adequately trained in ECMO methodology.*
> - *The SciMed membrane oxygenator has been used without complication for up*

[d] 21 CFR 870.4350 Cardiopulmonary Bypass Oxygenator was reclassified in 2001 from Class III to Class II with Special Controls.

to 32 days. Technical complications during long-term use are generally due to ineffective anticoagulation, which reduced oxygenator efficiency. Procedures lasting > 6 hours should include monitoring of blood compartment pressure drop and whole blood coagulation times, and inspection for thrombus formation and system component wear.

- *Condensate/water droplets may appear in the gas outlet port area; this has no significant effect on oxygenator performance.*
- *When normothermic perfusion is used for ECMO, the heat exchanger can be connected to the arterial side (outlet) of the oxygenator; arterial blood should enter the top of the heat exchanger.*
- *Use distilled or deionized water in the water bath circuit."*

Heat Exchangers

K884560 (cleared April 3, 1989 under 21 CFR 870.4240 Cardiopulmonary bypass heat exchanger, product code DTR, Class II)

ECMOtherm Heat Exchangers (SciMed):

Cleared Indications:

"The ECMOtherm heat exchanger is intended to be used in neonatal and pediatric ECMO procedures as an integral component in the extracorporeal circuit to maintain normothermia."

K873699 (cleared December 2, 1987 under 21 CFR 870.4240 Cardiopulmonary bypass heat exchanger, product code DTR, Class II)

Seabrook Medical Blood Warming Unit

Cleared Indications:

No specific "indications for use" statement was found (this was before FDA required Indications for Use Forms), however the labeling states that the Seabrook Medical Blood Warming Unit was designed specifically for ECMO procedures to treat cardiorespiratory insufficiency.

Cannula/Catheter

K895352 (cleared November 29, 2989 under 21 CFR 870.4210 Cardiopulmonary bypass catheter, cannula, tubing. product code DWF, Class II)

Kendall 14Fr Veno-venous Dual-Lumen Infant ECMO Catheter

Cleared indication:

> "The Kendall Dual-Lumen ECMO cannula is intended to be used as a single cannula for both venous drainage and reinfusion of blood in the right atrium, via the internal jugular vein during ECMO procedures."

K003288 (cleared June 8, 2001 under 21 CFR 870.1200 Diagnostic intravascular catheter, product code GBK, Class II)

Origen – Dual Lumen Cannulas - 12Fr and 15Fr

Cleared indication:

> "The OriGen Dual Lumen Cannula is indicated for the simultaneous drainage and reinfusion of blood through the internal jugular vein during ECMO procedures."

K081820 (cleared October 6, 2008 under 21 CFR870.4210 Cardiopulmonary bypass catheter, cannula, tubing. Product code DWF, Class II)

Avalon Elite Bi-Caval Dual Lumen Catheter

Cleared indication:

> "The Avalon Elite Bi-Caval Dual Lumen Catheter is intended for use as a single catheter for both venous drainage and reinfusion of blood via the internal jugular vein during extracorporeal life support procedures."

In summary, the devices that have been cleared with ECMO indications have been cleared under several different classification regulations. Part of our regulatory strategy is to ensure that there is consistency in review for the devices intended for ECMO, including 1) a consistent identification for the regulation that includes all of the devices/accessories necessary to perform ECMO, 2) defining long-term cardiopulmonary support as > 6 hours of support (since the same devices used for cardiopulmonary bypass are intended for short-term ≤ 6 hours of support), and 3) having all components used in ECMO procedures under one regulation and classified consistently based on current knowledge of the safety and effectiveness information available. Our regulatory strategy also takes into consideration the fact that all products intended for use in an ECMO circuit are devices that are currently on the market for short-term cardiopulmonary bypass procedures as Class II devices.

Classification History for 21 CFR 868.5610

A brief summary of the regulatory history for membrane lung devices for long-term pulmonary support devices is provided within this section.

1979 Proposed Rule and 1982 Final Rule

November 2, 1979 Proposed Rule (44 FR 63387)

This rule proposed membrane lung devices for long-term pulmonary support (i.e., ECMO) be classified into Class III (pre-market approval), because "…insufficient information exists to determine the adequacy of general controls, or to establish standards, to provide reasonable assurance of the safety and effectiveness of this device which is both life-sustaining and life-supporting." The Anesthesiology Device Classification Panel identified the following risks to health associated with the device:

- Thrombocytopenia leading to a tendency of increased bleeding;
- Hemolysis;
- Biocompatibility; and
- Inadequate gas exchange

Comments regarding this proposal were requested by January 2, 1980.

July 16, 1982 Final Rule (47 FR 31130)

No comments were received by January 2, 1980, so the proposed classification (Class III) was finalized. Membrane lung for long-term support was classified under 21 CFR Part 868 Anesthesiology Devices, Subpart F – Therapeutic Devices, 868.5610:

> ***§ 868.5610 Membrane lung for long-term pulmonary support.***
>
> ***(a) Identification. A membrane lung for long-term pulmonary support is a device used to provide to a patient extracorporeal blood oxygenation for longer than 24 hours.***
>
> ***(b) Classification. Class III (premarket approval).***

In 1987, FDA published a clarification in the codified language stating that no effective date had been established for the requirement for premarket approval for the membrane lung for long-term pulmonary support (52 FR 17735, May 11, 1987).

1995 515(i) Order (Call for Information) and 1998 Citizens Petition

August 14, 1995 515(i) Order (60 FR 41984)

This Order required the manufacturers of 27 Class III devices (including membrane lung devices for long-term pulmonary support (21 CFR 868.5610)), to submit to FDA a summary of "…all information known or otherwise available to them respecting such devices, including adverse safety or effectiveness information concerning the devices…in order to determine…whether the classification of the device should be revised, or whether a regulation requiring the submission of premarket approval applications (PMAs) for the device should be promulgated." Based on preliminary information, FDA identified the membrane lung for long-term pulmonary support (21

CFR 868.5610) as one of 27 remaining Class III devices not likely to be reclassified and most likely to require the submission of PMAs in the future.

February 13, 1998 Citizen's Petition - response to 60 FR 41984 (updated 62 FR 32352 to modify required response date from August 14, 1996 to February 14, 1998)

A Citizen's Petition recommending reclassification of the membrane lung for long-term pulmonary support (21 CFR 868.5610) from Class III to Class II, was submitted by a trade organization.

All risks identified in the original proposed rule (44 FR 63387, 1979) and additional risks identified by the submitter (see Discussion of Risks to Health section below) were addressed through proposed special controls (see Table 25 in Mitigations of Risks Section below).

No final rule was issued following the August 14, 1995 (amended June 13, 1997) FR Notice calling for information related to the classification of membrane lung devices for long-term pulmonary support (21 CFR 868.5610).

2009 515(i) Order (Call for Information) for Remaining Class III Pre-Amendments Devices

April 9, 2009 515(i) Order (74 FR 16214)

FDA issued an order requiring the manufacturers of the remaining Class III devices (including 868.5610 membrane lung for long-term pulmonary support) "…for which regulations requiring submission of premarket approval applications (PMAs) have not been issued…" to submit a summary of "…information known or otherwise available to them respecting such devices, including adverse safety or effectiveness information concerning the devices … in order to determine…whether the classification of the device should be revised to require the submission of a PMA or a notice of a completion of a Product Development Protocol (PDP), or whether the device should be reclassified into Class I or II." This information was requested to be submitted by August 7, 2009.

Industry Response

August 6, 2009 - Response to April 9, 2009 515(i) Call for Information - Medtronic Cardiovascular, Inc.

Medtronic submitted a response to the April 9, 2009 order for 21 CFR 868.5610 membrane lung for long-term pulmonary support. The information consisted of a copy of the previous citizen's petition (February 13, 1998), along with some updated information (no new risks to health were identified) and a new MDR analysis (see Summary of Evidence Section below). Medtronic is again suggesting that the devices (i.e., oxygenators) be reclassified into Class II (Special Controls), based on the history of the device, the proposed special controls to mitigate the list of risks associated with the device (proposed the same special controls identified in the 1998 citizen's petition), and 30+ year data from the ELSO Registry providing clinical information related to ECMO for all indications/conditions.

January 8, 2013 Proposed Order: Reclassification of the Membrane Lung for Long-Term Pulmonary Support

January 8, 2013 – Proposed Order(78 FR 1158).

FDA issued a proposed order recommending that the current regulation for membrane lung devices for long-term pulmonary support should be redefined to include all components of an extracorporeal circuit for long-term use (ECMO). Furthermore, FDA proposed that these devices be reclassified from class III (PMA) to class II (Special Controls) when an acute (reversible) condition prevents the patient's own body from providing the physiologic gas exchange needed to sustain life in conditions where imminent death is threatened by respiratory (e.g., meconium aspiration, congenital diaphragmatic hernia, pulmonary hypertension), or cardiorespiratory failure (resulting in the inability to separate from cardiopulmonary bypass following cardiac surgery) in neonates and infants.

Responses to this proposal were requested by April 8, 2013.

Industry Response

Comments were received from three sources:

1. 1 of 3 agreed with FDA's proposed reclassification of 21 CFR868.5610;
2. 1 of 3 requested clarification in the scope of the patient population and definitions identified for reclassification; and
3. 1 of 3 was concerned with the proposed regulation, processes, and scope in terms of the requirements for and the regulation of the new technology and expanded clinical use of ECMO for new unproven uses.

A summary of the comments received where there was a request for clarification (number 2 above) or where there were concerns regarding the proposed regulation (number 3 above) can be found below:

Maquet

Maquet aptly pointed out that the proposed order (published January 8, 2013) required additional clarification regarding the scope of the patient population and the conditions (cardiopulmonary or cardiac) identified for down-classification.

- Clarification was requested for the patient population(s) identified for the reclassification, e.g., infants/neonates and/or adults

FDA Response**:** FDA has identified neonates/infants where imminent death is threatened by cardiopulmonary failure (e.g., due to meconium aspiration, congenital diaphragmatic hernia, pulmonary hypertension) because FDA believes that the available data along with the practice of medicine indicate that ECMO is the standard of care for these reversible conditions. Where cardiopulmonary failure results in the inability to separate from cardiopulmonary bypass following cardiac surgery, FDA originally intended this for the neonatal/infant population only as well. However, since the statement as written in the proposed order can also be interpreted to include both the pediatric and adult populations, FDA decided to include all patient populations in our research efforts. FDA did not find enough evidence to support down-classification for the adult population for cardiopulmonary failure in failure-to-wean. However, the literature does potentially support the pediatric patient population for cardiopulmonary failure in failure-to-wean following cardiac surgery. As such, the original intent of down-classifying ECMO circuit components for reversible respiratory conditions and cardiopulmonary failure-to-wean in the neonates/infants and pediatric patient population has now been included in our reclassification proposal.

- Clarification was requested regarding whether the reclassification proposal was limited to cardiopulmonary conditions only, or cardiac conditions as well.

  FDA Response: The comment is correct in that the wording used is not consistent with the references used for support. As such, FDA acknowledges the inconsistency and would like to clarify and correct the wording to "ECMO is intended for patients with acute reversible respiratory or cardiorespiratory failure," and "…long-term pulmonary/cardiopulmonary support." Cardiac failure is not intended as part of the reclassification proposal due to lack of valid scientific evidence in support of the safety and effectiveness of ECMO in treating cardiac only conditions.

Public Citizen

Public Citizen had concerns related to the scope of the reclassification (patient population as well as indications), and also how the regulation would take newly designed devices and/or redesigned cleared devices into consideration with respect to assuring a safe and effective device. Below is a summary of the identified concerns and FDA response:

- "…it seems that ECMO devices, at least the versions dating from the 1980s-90s (the time period in which the four RCTs were conducted), have proven effective in increasing survival in term and near-term neonates with severe, reversible respiratory failure. We do not have sufficient knowledge of the design characteristics or functionality of devices that have come on the market since the 1990s to discern to what extent ECMO devices used in neonates today resemble the prior versions that demonstrated effectiveness in curbing neonate mortality."

FDA Response: Initial classification and reclassification recommendations are based on existing information for legally marketed devices and their predicates. Devices that are not currently on the market with ECMO labeling, would need to submit a 510(k) submission to FDA. The 510(k) decision-making process would be applied to determine whether the device has the same intended use and/or technological characteristics in comparison to the predicate device. If the device has a new intended use or different technological characteristics that raise different questions of safety and effectiveness in comparison to the predicate, the device would be ineligible for review through the 510(k) program. For the conditions noted in the reclassification (and also noted by Public Citizen), FDA believes that <u>ECMO has proven to be an effective therapy</u>. Each manufacturer pursuing ECMO marketing clearance for their device must provide sufficient non-clinical and in vivo data (to potentially include either prospective or retrospective clinical data or animal data if appropriate) to demonstrate substantial equivalence. Please also refer to the 'Introduction and Regulatory Reference Sheet'.

- Public Citizen puts forward the argument that "The absence of RCTs evaluating the relative benefits and risks of these therapies [pharmacologic and other mechanical interventions], precludes assessment of the benefit-to-risk profile of the ECMO therapy compared with other therapies in these [failure-to-wean] patients."

  FDA Comment: At this time, there appears to be lack of equipoise between ECMO and other potential therapies, suggesting that ECMO may be considered the standard of care for failure-to-wean in the pediatric patient population. FDA acknowledges that the evidence in this area is not as strong as in the previous category of respiratory failure in neonates/infants due to meconium aspiration, diaphragmatic hernia, and pulmonary hypertension; however, the therapeutic trend in this patient population appears to be ECMO, so we anticipate a lively discussion in this area at the Panel meeting.

- "…the FDA makes no mention of uses of ECMO devices other than those indications proposed for Class II designation. Commonly encountered uses in the literature include adults with acute respiratory distress syndrome (ARDS), children (non-neonates) with respiratory or cardiac failure, adults with cardiac failure unrelated to cardiac surgery, and patients in cardiac arrest."

  FDA Comment: Indications for use not identified in the reclassification proposal would be considered outside the scope of this proposal and would not be part of the reclassification efforts.

- Public Citizen points out that mechanical failure of ECMO circuit components is not well defined as a risk to health.

  FDA Comment: FDA agrees and is proposing some changes to the identified risks to health as noted below.

- “Inadequate gas exchange” is redefined as “Design flaws or mechanical failure of the oxygenator may result in inadequate gas exchange.”
- “Loss of mechanical integrity” is changed to “Mechanical failure” and is defined as “design flaws, mechanical integrity concerns, weakness in the connections or construction of the circuit components could lead to breaches in the circuit, performance failures, blood loss, etc., over the intended duration of use.

- Public Citizen states that “The FDA has not convened a subsection (b) device classification panel to consider the proposed reclassification of ECMO devices….”

  FDA Comment: The Federal Food, Drug and Cosmetic Act through the Food and Drug Administration Safety and Innovation Act (FDASIA) of 2012 changed the reclassification process and as such the purpose of this classification panel meeting is to seek additional input regarding the appropriate regulatory classification for this device, prior to finalization of the classification process.

- Public Citizen states, “…[can] the FDA reasonably be assured of the safety and efficacy of new ECMO devices without requiring PMAs, including data from testing the new devices in well-controlled clinical trials.”

  FDA Comment: Public Citizen agrees that there is evidence that ECMO is safe and effective in neonates/infants with severe respiratory failure. As such, it is the Agency’s responsibility to assure that new devices seeking clearance for ECMO will also demonstrate this same (or better) benefit/risk profile. The Safe Medical Devices Act (SMDA) of 1990 permitted the submission of clinical data as a Special Control for Class II devices. SMDA changed Class II from performance standards to special controls. Clinical data is in the definition of Class II in 21 CFR 860.3(c)(2):

  > “A device is in class II if general controls alone are insufficient to provide reasonable assurance of its safety and effectiveness and there is sufficient information to establish special controls, including the promulgation of performance standards, postmarket surveillance, patient registries, development and dissemination of guidance documents (**including guidance on the submission of clinical data in premarket notification submissions** in accordance with section 510(k) of the act), recommendations, and other appropriate actions as the Commissioner deems necessary to provide such assurance.”

  As such, in vivo data (which can include clinical data) will be part of the special controls necessary to demonstrate safety and effectiveness for any device seeking ECMO labeling (current and future designs).

- Public Citizen states, "Only by testing each new version of the device can the FDA ensure that newer versions are as safe and effective as previously approved counterparts."

  FDA Comment: The 510(k) flowchart asks whether the device has different technological characteristics as compared to the predicate device. If the new device has different technological characteristics that affect the safety and/or effectiveness of the device, then a risk analysis will be applied to determine the type of testing needed to address the concerns. This testing can range anywhere from simple bench testing, to animal testing, to the need for clinical data. If different types of safety/effectiveness questions are raised based on the technological differences, the newly designed device would be ineligible for the 510(k) process and be a Class III device, eligible for review through a PMA or the *de novo* process.

- Public Citizen claims that reclassification for some indications will reduce the incentive to undertake future studies for untested indications due to the availability of the devices for "off-label" use.

  FDA Comment: FDA does not regulate the practice of medicine. However, the manufacturer of the device is not permitted to sell, market or promote their device for any indication other than the cleared indication(s). If the manufacturer wishes to seek clearance for 'untested indications,' they will need to provide valid scientific evidence as part of a premarket submission for review by the Agency. If the 'untested indications' are actually a new intended use, then the manufacturer would need to submit either a PMA or *de novo*. In any circumstance, authorization from FDA would be necessary prior to marketing.

- Public Citizen would like assurance that those indications not identified in the regulation will require the submission of a PMA for marketing.

  FDA Comment: By identifying the patient populations and conditions in the new regulation, conditions that fall outside the proposed definition (e.g., cardiac failure, adult respiratory failure) would be considered new intended uses and as such considered Class III requiring an approved PMA or granting of a *de novo* request prior to marketing.

Discussion of Risks to Health

In **Table 1** below, FDA has identified the risks to health generally associated with the use of an extracorporeal circuit for long-term pulmonary support (including a membrane lung for long-term pulmonary support [21 CFR868.5610], as well as other components needed in the extracorporeal circuit).

- All *italicized information* was prepared from the list of risks identified by the original classification panel as stated in the original proposed rule – November 2, 1979 (44 FR 63387) – Proposed Rule Classification of Membrane Lung for Long-Term Pulmonary Support.

- All risks identified in normal font are the additional risks noted in the February 13, 1998 Citizen's Petition – response to 60 FR 41984 [updated 62 FR 32352] call for information.

- All risks in **bold** font are additional risks identified for the proposed expanded identification for 21 CFR8670.4100 Extracorporeal circuit and accessories for long-term pulmonary/cardiopulmonary support.

TABLE 1: ECMO Risks to Health

RISKS to HEALTH	
Thrombocytopenia	*Blood platelets important to the clotting cascade may be damaged by use of the device, resulting in a tendency toward increased bleeding.*
Hemolysis	*Red blood cells may be damaged by mechanical, material, or surface features of the extracorporeal circuit.*
*Adverse Tissue Reaction**	*The patient-contacting materials of the device may cause an adverse immunological or allergic reaction in a patient if the materials are not biocompatible.*
Inadequate Gas Exchange	*Design flaws or mechanical failure of the oxygenator may result in inadequate gas exchange.*[1]
Gas Embolism	Air may be introduced into the extracorporeal circuit and result in a gaseous embolism.
Mechanical Failure [2]	Design flaws, mechanical integrity concerns, weakness in the connections or construction of the circuit components could lead to breaches in the circuit (leaks), performance failures, blood loss, etc., over the intended duration of use.[3]
Hemorrhage	To keep blood from clotting in the extracorporeal circuit, anticoagulants are generally used and may cause increased bleeding during the procedure.
Hemodilution	**Dilution of the patient's blood volume may be caused by the priming of the ECMO circuit.**
Thrombosis/thromboembolism	**Blood clots may form within the extracorporeal circuit due to inadequate blood flow.**
Infection	**Defects in the design or construction of the device preventing adequate cleaning and/or sterilization may allow pathogenic organisms to be introduced and may result in infection.**
Mechanical injury to access vessels	**Mechanical injury to vessels may be caused acutely during access, or over time due to the long-term duration of use.**

* Adverse Tissue Reaction = Biocompatibility

1 Definition modified based on comments received for the January 8, 2013 proposed order

2 Mechanical Failure replaces "Loss of Mechanical Integrity" based on comments received for the January 8, 2013 proposed order.

3 Definition modified based on comments received for the January 8, 2013 proposed order.

The panel will specifically be requested to comment on the risks to health identified by FDA and whether these risks are appropriate, and/or whether there are additional risks to health that should be considered for these devices.

The special controls recommended to mitigate these identified risks are given in **Table 26** found in the section of this summary titled "Summary of FDA Recommendation."

Summary of Evidence

Medical Device Report (MDR) Analysis and Recalls

MDR Analysis

The Manufacturer and User Facility Device Experience (MAUDE) database was searched and several analyses were performed by FDA since the April 9, 2009 Order was published, to provide an awareness of the adverse events (AEs) and rates of AEs related to the devices used for ECMO.

Due to several limitations related to a MAUDE search for ECMO, the following searches differ by dates, devices, and search terms, in an attempt to get the best overall understanding of the device and patient problems that are experienced during long-term extracorporeal oxygenation. One of the biggest limitations includes the fact that ECMO procedures are performed using many cardiopulmonary bypass circuit devices (many of which are used off-label), so searching the MAUDE database using the ECMO product code BYS (oxygenator for long-term pulmonary support) only will not provide an accurate representation of the adverse events experienced with an ECMO circuit. For example, the following search was performed on BYS only:

> **A MAUDE search conducted on just the BYS product code identified 16 reports through 6/29/2012, including 2 injuries and 14 malfunctions. Most of the issues were identified as leaks and required replacement of a circuit component**.

Table 2 MDRs for BYS Product Code Only

Death	Injury	Malfunction	Other	Invalid	Total Reports
0	2	14	0	0	16

As such, the following product codes, dates and search terms were utilized in several combinations in the MAUDE searches (7 total), in an attempt to obtain a better understanding of the adverse events experienced during a long-term ECMO procedure and not for use during a short-term cardiopulmonary bypass procedure:

- **Dates**:
    - **January 1, 2005 – August 24, 2010** (initial FDA searches with analysis)
    - **January 1, 1999 – May 30, 2009** (chosen to match search performed by Medtronic)
    - **January 1, 2003 – June 30, 2013** (recent FDA search to update numbers only)

- **Product Codes**
    - BYS §868.5860 Membrane Lung for Long-Term Pulmonary Support

- DTZ §870.4350 Cardiopulmonary Bypass Oxygenator
- DWF §870.4210 Cardiopulmonary Bypass Vascular Catheter, Cannula, or Tubing
- DTQ §870.4220 Cardiopulmonary Bypass Heart Lung Machine Console
- DTR §870.4240 Cardiopulmonary Bypass Heat Exchanger
- DTM §870.4260 Cardiopulmonary Bypass Arterial Line Blood Filter
- DWB §870.4370 Roller-type Cardiopulmonary Bypass Blood Pump
- DWE §870.4390 Cardiopulmonary Bypass Pump Tubing
- DTN §870.4400 Cardiopulmonary Bypass Blood Reservoir

- **Search Terms**:
  - ECMO
  - **Manufacturers of currently cleared ECMO devices**
    - Medtronic
    - Scimed
    - Avalon
    - Origen
    - Kendall
    - Seabrook Medical

<u>MDR Searches One through Three</u>

The following three searches were performed with an analysis of patient and device problems, to provide an idea of the events that are reported for ECMO as defined by the original regulation – 21 CFR 868.5610 Membrane lung for long-term pulmonary support – i.e., the oxygenator:

MAUDE Search One

The MAUDE database was initially searched using the following criteria:

- January 1, 2005 through August 24, 2010
- Product Codes: BYS and DTZ

The initial MAUDE search yielded a total of 578 medical device reports (MDRs) including 503 Manufacturer Reports, 1 Distributor Report, 53 User Facility Reports and 21 Voluntary Reports. Malfunctions were the most frequently reported type of event, with 23 reported deaths (Table 3).

Table 3. Type of Event-MAUDE search 1

Death	Injury	Malfunction	Other	Invalid	Total Reports
23	89	450	11	5	578

An online analysis of these reports determined the most frequently reported device and patient problem codes (Tables 4 and 5). Please note, that multiple device and patient problems may be reported in each adverse event report, and therefore the total number of problems may exceed the number of MDRs. The most frequently reported device problems were related to replacement of the device (reason for device replacement unknown) and fluid leaks/leaks (Table 4). The most frequently reported patient problems were no impact to patient and blood loss (Table 5).

Table 4 Analysis of Device Problems

Rank	Count	Percent	Device Problem
1	229	19.49	Replace
2	132	11.23	Leak
3	115	9.79	Fluid Leak
4	104	8.85	Malfunction
5	79	6.72	Tears, rips, holes in device, device material

Table 5 Analysis of Patient Problems

Rank	Count	Percent	Patient Problem
1	248	29.52	No Consequences Or Impact To Patient
2	116	13.81	Blood loss
3	75	8.93	Surgery, prolonged
4	70	8.33	No patient Involvement
5	52	6.19	Unknown

MAUDE Search two

A second MAUDE search was performed (a "subset" of search one above) using the following criteria:

- January 1, 2005 through August 24, 2010
- Product Codes: BYS and DTZ, and
- variations of the manufacturer name Medtronic (the only manufacturer with and ECMO Oxygenator [DTZ] on the market)

The second MAUDE search yielded a total of 315 MDRs including 271 Manufacturer Reports, 34 User Facility Reports and 10 Voluntary Reports. Malfunctions were the most frequently reported Type of Event, with a significant number of patient injuries and 14 reported deaths (Table 6).

Table 6. Type of Event-MAUDE search 2

Death	Injury	Malfunction	Other	Invalid	Total Reports
14	59	236	5	1	315

An online analysis of these reports determined the most frequently reported device and patient problem codes (Tables 7 and 8). Please note, that multiple device and patient problems may be reported in each adverse event report, and therefore the total number of problem codes may exceed the number of MDRs. The most frequently reported device problems were related to replacement of the device (reason for device replacement unknown) and fluid leaks/leaks (Table 7). The most frequently reported patient problems were no impact to patient and prolonged surgery (Table 8).

Table 7 Analysis of Device Problems

Rank	Count	Percent	Device Problem
1	147	26.53	Replace
2	101	18.23	Leak
3	34	6.14	Fluid Leak
4	31	5.60	Other
5	29	5.23	Performance
	29	5.23	Poor gas exchange

Table 8 Analysis of Patient Problems

Rank	Count	Percent	Patient Problem
1	129	27.86	No Consequences Or Impact To Patient
2	64	13.82	Surgery, prolonged
3	35	7.56	Unknown
4	31	6.70	Blood loss
5	27	5.83	Death

MAUDE Search Three

A third MAUDE search was completed using the following criteria:
- January 1, 1999 through May 30, 2009 (to match Medtronic's MDR search terms)
- Product Codes: BYS and DTZ, and
- variations of the Manufacturer name Medtronic.

The third MAUDE search yielded a total of 600 MDRs including 535 Manufacturer Reports, 44 User Facility Reports and 21 Voluntary Reports. Malfunctions were the most frequently reported Type of Event, with a significant number of patient injuries and 32 reported deaths (Table 9).

Table 9 Type of Event- MAUDE search 3

Death	Injury	Malfunction	Other	Invalid	Total Reports
32	74	488	4	2	600

An online analysis of the 32 death reports was completed to determine the device problem codes that lead to patient deaths. The results of the analysis are presented in Table 10.

Table 10 Analysis of Device Problems- MAUDE search 3

Rank	Count	Percent	Device Problem
1	10	14.29	Replace
2	6	8.57	Device Issue
3	5	7.14	Leak
4	4	5.71	Fluid Leak
	4	5.71	Unknown
5	3	4.29	Air Leak
	3	4.29	Increase in pressure
	3	4.29	Restricted Flow
	3	4.29	Disconnection
	3	4.29	Use of Device Issue

Individual review of the death reports indicated that there were 7 pediatric deaths related to use of the oxygenator component. Five of the pediatric death reports were new reports not previously captured in MAUDE search One (1/1/05 – 8/24/10) due to the extended time period used for the search (1/1/99 – 5/30/09).

An online analysis of the 600 reports identified in this MAUDE search determined the most frequently reported device and patient problems (Tables 11 and 12). Please note, that multiple device and patient problems may be reported in each adverse event report, and therefore the total number of problem codes may exceed the number of MDRs. The most frequently reported device problems were related to replacement of the device (reason for device replacement unknown) and fluid leaks/leaks (Table 11). The most frequently reported patient problems were no impact to patient, prolonged surgery and blood loss (Table 12).

Table 11 Analysis of Device Problems - MAUDE search 3

Rank	Count	Percent	Device Problem
1	399	30.81	Replace
2	189	14.59	Leak
3	68	5.25	Fluid Leak
4	67	5.17	Performance
5	55	4.25	Increase in pressure

Table 12 Analysis of Patient Problems -MAUDE search 3

Rank	Count	Percent	Patient Problem
1	351	36.99	No Consequences Or Impact To Patient
2	76	8.01	Surgery, prolonged
3	64	6.74	Blood loss
	64	6.74	Unknown
4	61	6.43	Death
5	42	4.43	Oxygen Saturation, Low

MDR Searches Four through Seven

The following four MDR searches were performed recently, to both update numbers from searches 1 through 3 above (search 4 below), as well as to perform a search to include all ECMO circuit components to get a better understanding of the events experienced with ECMO since ECMO is carried out by an entire circuit of devices (searches 5 through 7):

MAUDE Search Four

A fourth MAUDE search was performed to update numbers. The search was completed using the following criteria:
- January 1, 2003 through June 30, 2013
- Product Codes: BYS, DTZ

The fourth MAUDE search yielded a total of 1340 MDRs including 15 Distributor Reports, 1173 Manufacturer Reports, 103 User Facility Reports and 49 Voluntary Reports. Malfunctions were the most frequently reported Type of Event, with 85 reported deaths (Table 13).

Table 13 Type of Event MAUDE Search 4

Reports By Source

Report Source	Death	Injury	Malfunction	Other	Invalid	Total
DISTRIBUTOR	5	6	2	0	2	**15**
MANUFACTURER	64	131	803	118	57	**1,173**
USER FACILITY	12	16	62	5	8	**103**
VOLUNTARY	4	21	20	1	3	**49**
TOTAL	**85**	**174**	**887**	**124**	**70**	**1,340**

The same search was carried out with the term ECMO applied in the text search as well, and 0 reports were identified.

MAUDE Search Five

A fifth MAUDE search was completed using the following criteria (includes all circuit device product codes, not just the ones that have ECMO clearance):
- January 1, 2003 through June 30, 2013
- Product Codes: BYS, DTZ, DWF, DTR, DTQ, DTM, DWB, DWE, DTN
- ECMO

The fifth MAUDE search yielded a total of 301 MDRs including 4 Distributor Reports, 200 Manufacturer Reports, 68 User Facility Reports and 29 Voluntary Reports. Malfunctions were the most frequently reported Type of Event, with 48 reported deaths (Table 14).

Table 14 Type of Event MAUDE Search 5

Reports By Source

Report Source	Death	Injury	Malfunction	Other	Invalid	Total
DISTRIBUTOR	2	1	0	0	1	**4**
MANUFACTURER	37	57	92	14	0	**200**
USER FACILITY	6	5	42	3	12	**68**
VOLUNTARY	3	14	9	1	2	**29**
TOTAL	**48**	**77**	**143**	**18**	**15**	**301**

MAUDE Search Six

A sixth MAUDE search was completed using the following criteria (a "subset" of search 5 above):

- January 1, 2003 through June 30, 2013
- Product Codes: BYS, DTZ, DWF, and DTR (device types with currently cleared ECMO labeling only), and
- ECMO

The sixth MAUDE search yielded a total of 254 MDRs including 4 Distributor Reports, 165 Manufacturer Reports, 57 User Facility Reports and 28 Voluntary Reports. Malfunctions were the most frequently reported Type of Event, with 40 reported deaths (Table 15).

Table 15 Type of Event MAUDE Search 6

Reports By Source

Report Source	Death	Injury	Malfunction	Other	Invalid	Total
DISTRIBUTOR	2	1	0	0	1	**4**
MANUFACTURER	31	49	79	6	0	**165**
USER FACILITY	4	4	38	3	8	**57**
VOLUNTARY	3	13	9	1	2	**28**
TOTAL	**40**	**67**	**126**	**10**	**11**	**254**

MAUDE Search Seven

A seventh MAUDE search was completed using the following criteria (a "subset" of Search 6 above):

- January 1, 2003 through June 30, 2013
- Product Codes: BYS, DTZ, DWF, DTR
- ECMO

- Manufacturers Scimed, Medtronic, Avalon, Origen, Kendall, Seabrook Medical (all marketed devices with cleared ECMO labeling)

The seventh MAUDE search yielded a total of 10 MDRs including 1 Manufacturer Report, 4 User Facility Reports and 5 Voluntary Reports. Malfunctions were the most frequently reported Type of Event, with 3 reported deaths (Table 16).

Table 16 Type of Event MAUDE Search 7

Reports By Source

Report Source	Death	Injury	Malfunction	Other	Invalid	Total
DISTRIBUTOR	0	0	0	0	0	**0**
MANUFACTURER	0	0	1	0	0	**1**
USER FACILITY	2	0	2	0	0	**4**
VOLUNTARY	1	2	2	0	0	**5**
TOTAL	**3**	**2**	**5**	**0**	**0**	**10**

In summary, it is difficult if not impossible, to discern an accurate understanding of the event rates (device and clinical) that may be attributable to devices used for ECMO, due to voluntary reporting, off-label use of cardiopulmonary bypass components, and lack of a specific duration of use associated with the term extracorporeal membrane oxygenation (ECMO), i.e., can be used to imply both short-term as well as long-term durations of use. However, the numbers are quite small, especially when one focuses on the searches that included specific devices and manufacturers of devices labeled for ECMO (Searches 2, 3 and 7 above). Additionally, the device events noted in the analyses for searches 1 through 3 represent a set of events that can be evaluated via non-clinical and in vivo evaluation to demonstrate safety and effectiveness for the indications being proposed for reclassification.

Recalls

The following table (Table 17) represents a list of device recalls for all ECMO circuit components (i.e., product codes BYS, DTZ, DWF, DTR, DTQ, DTM, DWB, DWE, DTN - similar to MDR search 5 above). Since recalls typically reflect design controls or manufacturing issues that would apply regardless of the use of the device, these recalls do not necessarily reflect failures specific to ECMO use (as these circuit components are also used for cardiopulmonary bypass). It should be noted that recalls are classified into a numerical designation (I, II or III) by the FDA to indicate the relative degree of health hazard presented by the product being recalled, with Class I being the most severe.[e]

Table 17 Recalls for ECMO Circuit Devices

	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	Total
Class I Recalls	0	0	0	0	1	0	0	0	1	0	0	**2**
Class II Recalls	5	6	9	21	17	12	3	16	21	28	6	**144**
Class III Recalls	1	1	2	4	5	1	0	1	2	1	0	**18**
Total	**6**	**7**	**11**	**25**	**23**	**13**	**3**	**17**	**24**	**29**	**6**	

Literature Review

The literature was reviewed for the use of ECMO for cardiopulmonary and pulmonary failure, in infants/neonates (< 2 years old), for imminent death and a potential reversible condition for the following indications for use:

1. Meconium Aspiration Syndrome (MAS)
2. Congenital Diaphragmatic Hernia (CDH)
3. Primary Pulmonary Hypertension of the Newborn (PPHN)
4. Failure to Wean (postcardiotomy shock) from cardiopulmonary bypass (FTW)

In addition, a literature review was conducted for ECMO for cardiopulmonary failure in failure to wean (postcardiotomy shock) in adults (≥ 21 years old).

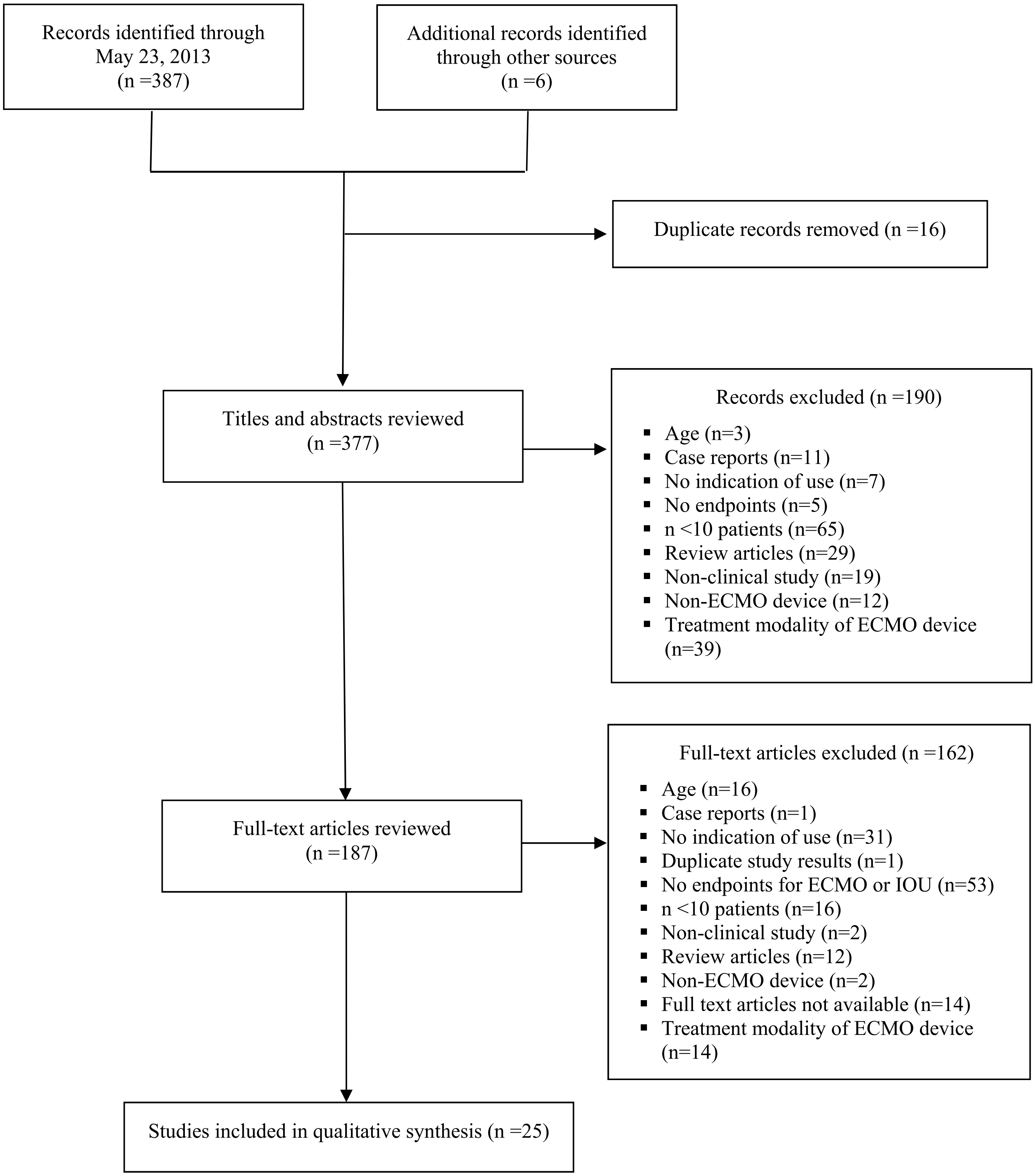
Methodology

Figure 2 presents the full diagram of article retrieval and selection. In summary, 387 articles were identified from PubMed; 16 duplicate articles were removed. Six additional records were identified from one of the references identified in the search[1]. A total of 377 abstracts and titles were reviewed, and 190 were excluded for the following reasons: case reports (n=11), studies with <10 patients (n=65), non-systematic reviews (n=29), did not study the relevant age groups (n=3), did not provide results for ECMO or indications for use (n=12), were non-clinical studies (n=19), evaluating non-ECMO devices (n=12), or evaluated treatment modalities for ECMO (n=39).

[e] Please refer to FDA's website for more information about recalls (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/RecallsCorrectionsAndRemovals/default.htm)

The full-text of the remaining 187 articles were examined for eligibility, of which 162 were excluded for the following reasons: case reports (n=1), studies with <10 patients (n=16), non-systematic reviews (n=12), did not provide results for ECMO or indications for use (n=53), relevant age groups (n=16), were non-clinical studies (n=2), evaluating non-ECMO devices (n=2), evaluating treatment modalities for ECMO (n=14), were not for the indications for use of interest (n=31), presented duplicate results (n=1), or full-text was not available (n=14). Thus, 25 full-text articles remained for detailed assessment in this review. The results of the UK Collaborative ECMO Trial[2,3] are summarized as one study (Table 17 and Appendix B).

Figure 2 - Flow diagram of article retrieval and selection



Nine of the studies included were conducted in the United States[5,8-10,14,17,21,22,26] and seven were from an international registry of the Extracorporeal Life Support Organization (ELSO).[4,7,12,13,19,20,23] The study designs from these studies included a randomized clinical trial (RCT),[2,3] a meta-analysis,[18] two cross-sectional,[11,15] one before/after,[5] and the rest were case series (Table 18).

Table 18 Study design of all publications included within this report (n=24)

Author (Year)	Study Design	Study Location
Meconium Aspiration Syndrome (MAS)		
Gill (2002)[4]	Case Series/ELSO[†] Registry	International
Graves (1989)[5]	Before/After	United States
Karimova (2009)[6]	Case Series	United Kingdom
Radhakrishnan (2007) [7]	Case Series/ELSO Registry	International
UK Collaborative ECMO Trial[2,3]	Randomized Clinical Trial	United Kingdom
Young (1997)[8]	Case Series	United Kingdom
Congenital Diaphragmatic Hernia (CDH)		
Aly (2010)[9]	Case Series	United States
Antunes (1995)[10]	Case Series	United States
The Congenital Diaphragmatic Hernia Study Group (CDHSG) (2009)[11]	Cross-sectional Study	International
Dimmitt (2001)[12]	Case Series/ELSO Registry	International
Dyamenahalli (2013)[13]	Case Series/ELSO Registry	International
Grist (2010)[14]	Case Series	United States
Hanekamp (2003)[15]	Cross-sectional Study	Netherlands
Jaillard (2003)[16]	Case Series	France
Karimova (2009)[6]	Case Series	United Kingdom
Kugelman (2003)[17]	Case Series	United States
Morini (2006)[18]	Meta-analysis	International
Ryan (1994)[19]	Case Series/ELSO Registry	International
UK Collaborative ECMO Trial[2,3]	Randomized Clinical Trial	United Kingdom
Primary Persistent Pulmonary Hypertension of the Neonate (PPHN)		
Karimova (2009)[6]	Case Series	United Kingdom
Lazar (2012)[20]	Case Series/ELSO Registry	International
Young (1997)[8]	Case Series	United States
Infant Failure to Wean (FTW)		
Bhat (2013)[21]	Case Series	United States
Hamrick (2003)[22]	Case Series	United States
Sherwin (2012)[23]	Case Series/ELSO Registry	International
Adult Failure to Wean (FTW)		
D'Alessandro (2011)[24]	Case Series	France
Hsu (2010)[25]	Case Series	Taiwan
Muehrcke (1995)[26]	Case Series	United States

Abbreviation: ELSO: Extracorporeal Life Support Organization.

Review

Meconium Aspiration Syndrome (MAS)

Six articles were identified with relevant data on the use of ECMO for cardiopulmonary failure in infants/neonates for Meconium Aspiration Syndrome (MAS) (Table 2). The UK Collaborative ECMO Trial, a RCT among 69 infants with severe respiratory failure due to MAS, observed a difference in the survival to discharge of the infants that received ECMO compared to those that received conventional management (CM) (81% vs. 57%, $p<0.05$).[2] At age 4, the percentage of infants that were dead or severely disabled among those treated with ECMO and those that received CM was 22% and 43%, respectively.[3] The only other study with a comparison group identified is a study, conducted in the United States, where survival was compared before and after the availability of ECMO.[5] Survival among the 10 patients from the pre-ECMO availability period was 30% compared to 93% ($p<0.001$) among the 28 patients when ECMO was available.[5] This study did not follow-up the patients after they were discharged from the hospital. Timeframe for survival is assumed to be in-hospital/at discharge.

MAS data from the international registry from ELSO was analyzed in three studies. Gill et al.[4] observed that survival at discharge was 94% among 3,235 ELSO registry patients. Survival was similar between infants grouped by time from birth to ECMO. The other observational study that reported information on survival at discharge reported that 97% of the children treated with ECMO survived.[6]

Radhakrishnan used ELSO registry data from 572 patients and observed 1.90 complications per patient.[7] The most complications per patient observed were mechanical (0.65 ± 0.05), hematologic (0.23 ± 0.02), and renal (0.21 ± 0.02). Survival or major causes of death were not reported in the study (Appendix B).

Congenital Diaphragmatic Hernia (CDH)

ECMO use for cardiopulmonary failure in infants/neonates for CDH was identified in one RCT,[2,3] 11 observational studies[6,9-17,19] and one meta-analysis.[18] The meta-analysis identified two RCTs, of which one is the UK Collaborative ECMO Trial included in this literature review[2,3] with 35 CDH patients, and the other study with a total of 4 CDH patients, 2 in each arm. Additionally, the meta-analysis identified observational studies that assessed ECMO use and survival; 19 studies with outcomes for early mortality (before discharge) and 8 for late mortality (after discharge).

In the meta-analysis, the results from the RCTs showed higher short-term survival among infants with CDH treated with ECMO compared to infants randomized to conventional mechanical ventilation (CMV) (35% vs. 10.5% $p<0.05$). Although survival after discharge was higher among infants treated with ECMO (25%) compared to CMV (5%), this difference was not statistically significant. The UK Collaborative ECMO Trial information also showed that at age 4, 11% of the infants treated with ECMO were alive and not severely disabled compared to 0% of infants that received CMV.[3] The results of the observational studies for short- and long-term survival were very similar, around 65% for infants treated with ECMO and ~44% for infants not treated with ECMO ($p<0.001$).[18]

Similar survival results were reported in the observational studies identified in this literature review. Survival to discharge was 52% among 2,257 children included in the ELSO registry from 1990-1999,[12] and 61% among 636 patients from the Congenital Diaphragmatic Hernia Study Group registry.[11] Among infants with CDH and congenital heart disease from the ELSO registry study, survival to discharge increased from 29% in 1973-1992 to 47% in 1998-2010.[13,19]

Complications from ECMO have also been reported using data from the ELSO registry, with the most commonly reported complications being hemofiltration (16%), cardiac stunning (13.1%), seizures (12.3%), and cerebral infarction (10.5%).[12] Complications at two years after ECMO use among 18 out of 26 French surviving children included chronic lung disease (56%), gastroesophageal reflux (50%), growth retardation (44%), and developmental delays (17%).[16] Twenty-two percent of these children recovered without sequelae.

Primary Persistent Pulmonary Hypertension of the Neonate (PPHN)

Three studies were identified that examined ECMO use for cardiopulmonary failure in infants/neonates with Primary Persistent Pulmonary Hypertension.[6,8,20] Survival results from more than 1,500 ELSO registry patients from 2000-2010 showed that, in general, 81% of the patients on ECMO for PPHN survived, but survival was dramatically reduced with increased duration of ECMO support (Table 2).[20] Major causes of death included lack of lung recovery (49%) and organ failure (21%). Out of the 74% neonates with complications, cardiovascular (32%) and mechanical (26%) complications were reported the most.

Failure to Wean (FTW)

<u>Neonates/Infants</u>
In this review, three case series studies evaluated the survival of infants that had ECMO support due to failure to wean (postcardiotomy shock) from cardiopulmonary bypass.[21-23]

In one study, 67% of 39 infants, all weighing 3 kgs or less, survived at 30 days,[21] whereas among infants with congenital heart disease, survival among ECMO users for FTW ranged between 34% to 38%.[22,23]

Adults

Among adults, three case series studies evaluated the use of ECMO for cardiopulmonary failure in failure to wean.[24-26] One study, conducted in Taiwan, evaluated 51 cardiac surgery patients unable to wean from CPB and experiencing postcardiotomy cardiogenic shock.[25] Their hospital, 30-day, and 1-year survival rates were 33%, 51%, and 29%, respectively. On average, these patients stayed in the hospital 26.1 days (± 22). The major causes of death were pulmonary infections and the majority of the complications included acute renal failure (75%), femoral bleeding (39%), and haematuria (33%).[25] A similar 1-year survival (33%) was found among isolated cardiac transplant patients unable to wean from cardiopulmonary bypass in France.[24] Survival to discharge in a study of 15 patients in the US was 47% with half of those patients dying from cardiac death and the other half from multiple organ failure.[26]

Summary from Literature Review

There is a benefit in survival at discharge with the use of ECMO, compared to conventional management, for cardiopulmonary failure in infants/neonates for MAS and CDH. CDH patients receiving ECMO had a higher survival after hospital discharge compared to CDH patients receiving conventional mechanical ventilation (CMV). The data does not provide evidence to support a benefit for survival after hospital discharge or longer for patients with MAS. Conclusions on the benefit in survival of use of ECMO for cardiopulmonary failure in infants/neonates for PPHN and for failure to wean in infants and adults cannot be reached based on the published literature alone due to the lack of studies with a comparison group and also in the inconsistency in the adverse event reporting from the identified publications.

Clinical Evidence

Clinical need for therapy

ECMO clinical uses under consideration for reclassification by this panel include situations in neonates and infants where there is insufficient cardiorespiratory function to maintain life. Neonatal respiratory failure affects 2% of all live births, and is responsible for over one third of all neonatal mortality.[f] For these patients, ECMO is indicated for

[f] Steinhorn, RH. Neonatal Pulmonary Hypertension. Pediatr Crit Care 2010; 11:S79-S84

situations where the patient has already failed medical therapy, death is imminent due to the acute effects of cardiorespiratory failure, the underlying causative pathology results in temporary or reversible cardiopulmonary dysfunction (no expected ongoing insult or progression post-treatment), and the cardiopulmonary abnormalities and their resulting effects on general end organ function are recoverable.

Clinical rationale for ECMO

There are two types of ECMO – venoarterial (VA) and venovenous (VV). Both provide respiratory support, but only VA ECMO provides hemodynamic support. ECMO is a last resort therapy, instituted in neonates and infants only after all other reasonable avenues of appropriate medical therapy have been exhausted (estimated mortality for patients on ECMO exceeds 80%) or when it is judged that the time needed for medical measures to take effect is lacking. Modern medical therapy may include not only improved mechanical ventilation strategies, but also inhalation agents and pharmacologic measures aimed at reducing pulmonary vascular resistance. Due to size constraints, primary cardiac failure, as would be encountered post-cardiotomy, is primarily treated by ventilator and pharmacologic support, and measures for temporary adjunctive intravascular support such as intraaortic balloon pump are unsuitable for use in this age group. Though the Berlin Heart EXCOR was recently approved for a Bridge to Transplant Indication, its safety and probable benefit for the acute treatment of reversible cardiopulmonary failure post-cardiotomy is unknown.

Clinical Indications - Neonatal Respiratory Failure

Persistent pulmonary hypertension of the newborn (PPHN)

Persistent pulmonary hypertension (PPHN) complicates the course of approximately 10% of infants with respiratory failure regardless of the source, and is a source of considerable mortality and morbidity in this population.[f] The prevalence of PPHN has been estimated at 2 per 1000 live births. Although elevated pulmonary vascular resistance (PVR) and systemic pulmonary artery pressures are a normal and necessary state for the fetus where the placenta is the organ of gas exchange, PPHN occurs when the dramatic cardiopulmonary transition which normally occurs at birth to facilitate the transition to gas exchange by the lung fails to occur. This transition is normally characterized by a rapid fall in PVR and pulmonary artery pressure, and a 10-fold rise in pulmonary blood flow, and its failure (i.e., PPHN) results in often severe right-to-left shunting of blood through fetal circulatory pathways. This persistence of the fetal circulation leads to severe hypoxemia that may be unresponsive to conventional respiratory support or medical therapy aimed at lowering pulmonary vascular resistance. Specific tools in the acute treatment of severe PPHN include modern ventilatory strategies, and medical therapy including inhaled nitric oxide or intravenous agents aimed at lowering pulmonary vascular resistance such as sildenafil, bosentan, and prostacyclin.

PPHN can be generally characterized as one of three types:

1) the abnormally constricted pulmonary vasculature due to lung parenchymal diseases such as meconium aspiration syndrome, respiratory distress syndrome, or pneumonia;
2) the lung with normal parenchyma and remodeled pulmonary vasculature, also known as idiopathic PPHN; or
3) the hypoplastic vasculature as seen in congenital diaphragmatic hernia.

Neonatal pulmonary hypertension differs from pediatric pulmonary hypertension in that it resolves in the majority of infants, and has not been associated with genetic factors. Certain drugs (NSAIDs and SSRIs), especially when taken in the third trimester, have been associated with an increased incidence of idiopathic PPHN.[f]

The goal of initial mechanical ventilation is to improve oxygenation, achieve normal lung volumes, and to avoid the adverse effects of high or low lung volumes on PVR. Failure of conventional ventilatory management for PPHN Types 1 and 2 has historically has been treated with initiation of ECMO therapy.

ECMO for Treatment of PPHN Types 1 and 2 – Standard of Care

A Cochrane review and meta-analysis[g] of four randomized clinical trials was undertaken to determine whether ECMO used for neonates with severe respiratory failure is clinically effective (especially in terms of mortality and later childhood disability) compared to conventional ventilatory support. Trials relying on a range of physiological parameters to identify infants who had "severe but potentially reversible respiratory failure" (e.g., PaO2 <40mmHg or pH <7.15 for two hours), as well as those using the criterion of an oxygenation index of >40 to select patients were all included. Four randomized clinical trials were identified which satisfied the above criteria and entered infants with severe but potentially reversible respiratory failure, aged less than 28 days, with gestation at birth of 34 weeks or more were included. The majority of patients in these trials did not have congenital diaphragmatic hernia as the primary diagnosis either because this was an exclusion criterion (Boston and Syracuse) or because the numbers with this primary diagnosis were relatively small (1/12 in the Michigan trial and 35/185 in the UK trial). Outcome measures focused on mortality, disability and, in the case of the UK trial, use of health service resources.

For death before discharge home, each of the four trials showed a strong benefit of ECMO, but as the three US trials were all very small, the size of effect (typical relative risk (RR) 0.44) was overwhelmingly determined by the UK trial and the 95% CI was very tight (0.31 to 0.61), a highly statistically significant benefit ($p < 0.00001$). This can

[g] Mugford M, Field ED. Extracorporeal membrane oxygenation for severe respiratory failure in newborn infants (Review). Evid.-Based Child Health 5: 241–298 (2010)

also be expressed as a difference in rates of -0.32 (95% CI, -0.44 to -0.20), implying **only three babies need to be treated with ECMO rather than conventional ventilation to prevent one death.** The balance of benefits overall were strongly in favor of ECMO for this outcome. Tables 19-22 summarize the results from the Cochrane review.

Table 19: All Infants, Death before discharge

Analysis 1.1. Comparison 1 All eligible infants, Outcome 1 Death before discharge home.

Review: Extracorporeal membrane oxygenation for severe respiratory failure in newborn infants

Comparison: 1 All eligible infants

Outcome: 1 Death before discharge home

Study or subgroup	ECMO n/N	Conventional n/N	Weight	Risk Ratio M-H,Fixed,95% CI
Boston 1989	0/9	4/10	6.3 %	0.12 [0.01, 2.00]
Michigan 1985	0/11	1/1	3.8 %	0.06 [0.00, 0.94]
Syracuse 1992	1/15	6/13	9.5 %	0.14 [0.02, 1.05]
UK 1996	28/93	54/92	80.3 %	0.51 [0.36, 0.73]
Total (95% CI)	**128**	**116**	**100.0 %**	**0.44 [0.31, 0.61]**

Total events: 29 (ECMO), 65 (Conventional)

Heterogeneity: Chi^2 = 4.84, df = 3 (P = 0.18); I^2 =38%

Test for overall effect: Z = 4.76 (P < 0.00001)

Risk Ratio M-H,Fixed,95% CI

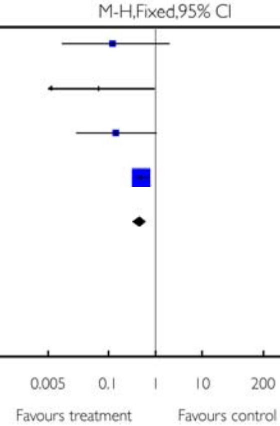


Table 20: Infants Without Congenital Diaphragmatic Hernia: Death before Discharge

Analysis 2.1. Comparison 2 Infants without congenital diaphragmatic hernia as principal diagnosis, Outcome 1 Death before discharge home.

Review: Extracorporeal membrane oxygenation for severe respiratory failure in newborn infants

Comparison: 2 Infants without congenital diaphragmatic hernia as principal diagnosis

Outcome: 1 Death before discharge home

Study or subgroup	ECMO n/N	Conventional n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Boston 1989	0/9	4/10		8.5 %	0.12 [0.01, 2.00]
Michigan 1985	0/10	1/1		5.1 %	0.06 [0.00, 1.02]
Syracuse 1992	1/15	6/13		12.8 %	0.14 [0.02, 1.05]
UK 1996	15/75	37/75		73.6 %	0.41 [0.24, 0.67]
Total (95% CI)	**109**	**99**		**100.0 %**	**0.33 [0.21, 0.53]**

Total events: 16 (ECMO), 48 (Conventional)
Heterogeneity: $Chi^2 = 3.17$, df = 3 (P = 0.37); I^2 =5%
Test for overall effect: Z = 4.58 (P < 0.00001)

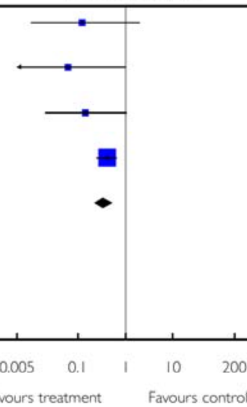


Table 21: Infants Without Congenital Diaphragmatic Hernia: Death before Age One

Analysis 2.2. Comparison 2 Infants without congenital diaphragmatic hernia as principal diagnosis, Outcome 2 Death in the first year of life.

Review: Extracorporeal membrane oxygenation for severe respiratory failure in newborn infants

Comparison: 2 Infants without congenital diaphragmatic hernia as principal diagnosis

Outcome: 2 Death in the first year of life

Study or subgroup	ECMO n/N	Conventional n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Syracuse 1992	2/15	6/13		14.8 %	0.29 [0.07, 1.19]
UK 1996	17/75	37/75		85.2 %	0.46 [0.29, 0.74]
Total (95% CI)	**90**	**88**		**100.0 %**	**0.43 [0.28, 0.68]**

Total events: 19 (ECMO), 43 (Conventional)
Heterogeneity: $Chi^2 = 0.37$, df = 1 (P = 0.54); I^2 =0.0%
Test for overall effect: Z = 3.62 (P = 0.00029)

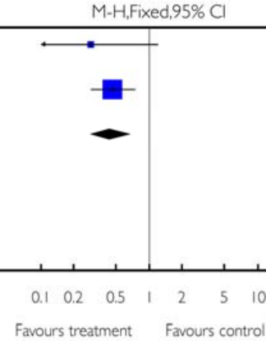


Table 22: All Infants: Death or Disabililty at Age Four

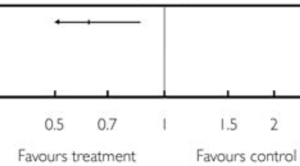
Analysis 1.26. Comparison 1 All eligible infants, Outcome 26 Death or severe disability at 4 years of age.

Review: Extracorporeal membrane oxygenation for severe respiratory failure in newborn infants

Comparison: 1 All eligible infants

Outcome: 26 Death or severe disability at 4 years of age

Study or subgroup	ECMO n/N	Conventional n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
UK 1996	34/93	54/92		0.62 [0.45, 0.86]



Cochrane Conclusions: *"The potential for acute problems related to the ECMO circuit and the inevitable disruption to the cerebral circulation led many to make the broad assumption that there was an inherent risk attached to the use of ECMO which would inevitably result in increased morbidity. These concerns have not been born out. Since the risks are undeniable it would appear that the damaging effect of prolonged exposure to aggressive conventional therapy as used in the 1990s are even greater. Although there is a clear benefit for the ECMO policy, the overall results showed overall nearly half of the children had died or were severely disabled at four years of age, reflecting the severity of their underlying conditions.* ***A policy of using ECMO in mature infants with severe but potentially reversible respiratory failure would result in significantly improved survival without any increased risk of severe disability amongst survivors****. The situation for babies with diaphragmatic hernia is less clear since, despite their common underlying anomaly, they do not represent a homogeneous group. It would appear that ECMO offers short term benefits but the overall effect of employing ECMO in this group is not clear."*[g]

Since this original meta-analysis, the approval of inhaled nitric oxide and use of high frequency ventilation has dramatically changed treatment for PPHN. These additional measures should be undertaken prior to initiation of ECMO therapy with the major goal being avoidance of ECMO. Although these additional measures have resulted in demonstrable decreases in the need for ECMO, they have not reduced mortality which remains at 15-20%. Neonates with Types 1 and 2 PPHN failing medical therapy continue to have high survival rates with ECMO support (>80%). The evidence for additional specific treatments for PPHN, especially Types 1 and 2, are outlined below (Table 23):

Table 23: Specific Treatments and Level of Evidence for PPHN[f]

Recommendations for Treatment of Neonatal Pulmonary Hypertension

Pulmonary Vasodilators:

Inhaled Nitric Oxide:

Inhaled Nitric Oxide should be initiated at 20 ppm for neonates with PPHN or hypoxemic respiratory failure when the oxygenation index exceeds 25. (Class I, Level A)

Sildenafil:

Limited evidence suggests that sildenafil may produce selective vasodilation in infants with PPHN. (Class IIb, Level B)

Other Supportive Modalities

Extracorporeal Life Support (ECLS or ECMO):

Cannulation for ECMO support should be considered for term and near-term neonates with pulmonary hypertension and/or hypoxemia that remains refractory to iNO after optimization of respiratory and cardiac function. (Class I, Level A)

High Frequency Ventilation:

In neonates with parenchymal lung disease (eg, meconium aspiration syndrome, respiratory distress syndrome, pneumonia), high frequency ventilation is often useful to promote lung expansion and enhance the effect of inhaled nitric oxide in infants. (Class IIa, Level B)

Surfactant:

Administration of surfactant may promote lung expansion and reverse surfactant inactivation associated with parenchymal lung disease. (Class IIa, Level A).

Alkalosis:

Alkalosis induced by hypocarbia or infusions of alkali may result in transient improved oxygenation. However, this practice is not recommended because of the lack of demonstrated benefit, and the potential for lung and cerebral injury. (Class III, Level B).

For the majority of cases of PPHN, the outcome depends on the pulmonary vascular response to treatment for the primary condition. A query of the ELSO registry for all neonates (0-31 days of life [DOL]) with a diagnosis of PPHN treated between January 2000 and December 2010 reveals that, once initiated, the mortality risk of ECMO therapy is increased by prematurity, and profound acidosis and/or hypoxemia prior to initiation of ECMO, and that delayed (initiation $\geq$ Day of life 5) or prolonged ($\geq$7 d) ECMO support is associated with a higher risk of mortality (Table 24).[h]

[h] Lazar DA, et al. The use of ECMO for persistent pulmonary hypertension of the newborn: A decade of experience Jour Surg Res 2012;177; 263-267

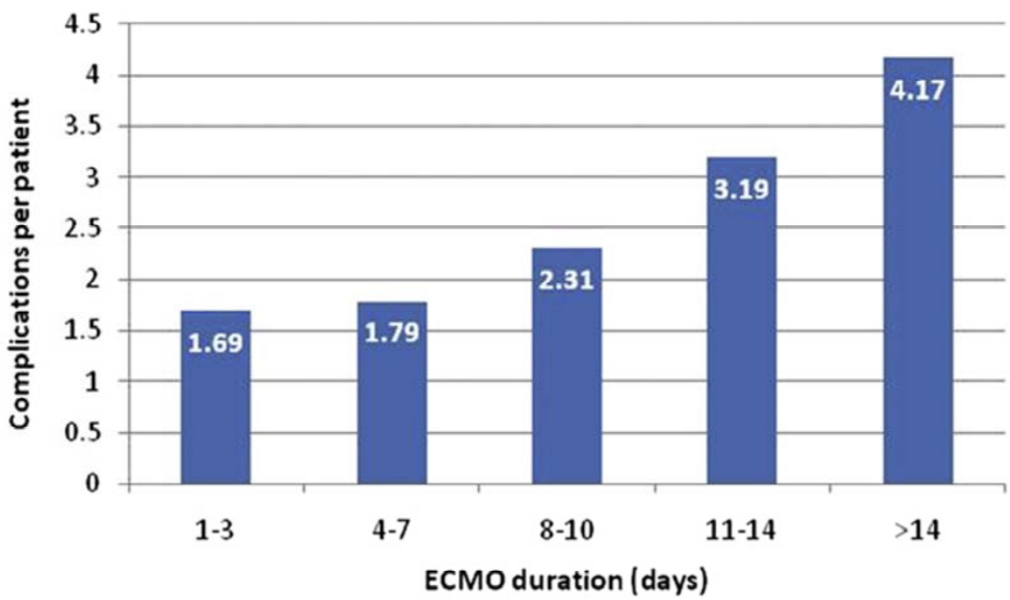
Table 24: Multivariate analysis comparing survivors and non-survivors with PPHN receiving ECMO

Variable	Odds of neonatal death		
	Odds ratio	95% confidence interval	*P* value
Gestational age < 37 wk	1.7	1.2–2.5	<0.01
pH ≤ 7.20	1.5	1.1–2.1	0.02
SaO_2 ≤ 65%	1.5	1.1–2.1	0.01
ECMO initiated ≥ DOL 5	1.8	1.2–2.6	<0.01
Duration of ECMO ≥ 7 d	3.4	2.5–4.7	<0.01

Data depict the odds of neonatal death among those with PPHN.

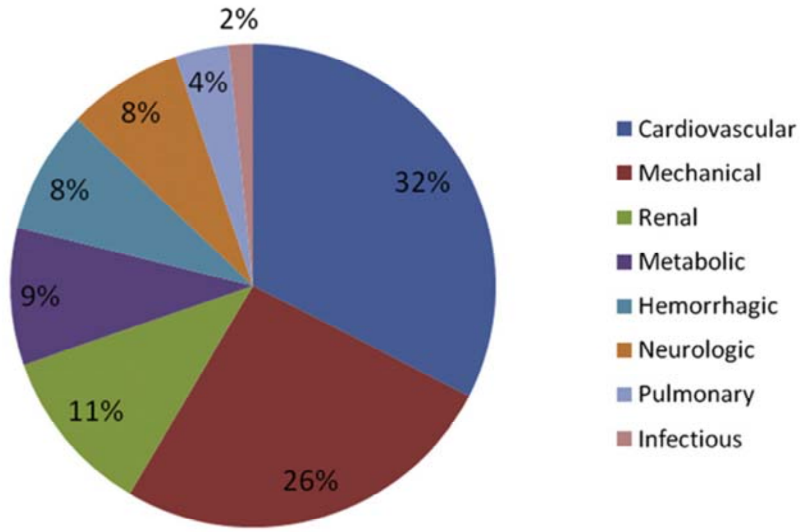
Prolonged ECMO was also found to be predictive of an increased incidence of complications per neonate over time (Figure 3).

Figure 3: ECMO duration vs Complications per neonate – PPHN



These complications were wide ranging in nature and affected numerous organ systems (Figure 4).

Figure 4. Distribution of ECMO Complications - PPHN



The authors conclude that the association of significant physiologic derangement with poor survival may be an impetus to initiate ECMO support before the development of severe physiological derangement in neonates with PPHN, and that non-survivors may have disease pathology distinct from PPHN (e.g., pulmonary dysplasia or hypoplasia) that is associated with a delayed or insidious onset of abnormalities that are more severe than those of survivors.

Congenital Diaphragmatic Hernia (CDH)

CDH requires separate discussion due to its complex nature and lower survival rates for all therapies, including ECMO. With the advent of high frequency ventilation and inhaled nitric oxide (iNO) for PPHN Types 1 and 2, CDH (PPHN Type 3) is now the primary indication for ECMO in neonates[i]. CDH is a developmental defect of the diaphragm that allows abdominal viscera to herniate into the chest. The volume of herniated contents may be small or large enough to contain most of the gut, spleen, or liver. Because herniation occurs during a critical period of lung development when bronchial and pulmonary artery branching occurs, lung compression by the herniated bowel results in variable degrees of pulmonary hypoplasia. Structural alterations in CDH lungs include a decrease of the total arteriolar cross-sectional area and a significant adventitial and medial wall thickening in pulmonary arteries of all sizes, with abnormal muscularization of the small pre-acinar and intra-acinar arterioles, leading to a persistent pulmonary hypertension (PPHT). Pulmonary vascular abnormalities in CDH result in a

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[i] Bartlett RH et al. Current Status of ECMO for Cardiopulmonary Failure. Minerva Anestesiol2010;76:534-540

decreased number of pulmonary arteries per unit of lung volume and in the peripheral muscularization of small arteries, with medial and adventitial thickening. The probability of survival in children born with CDH is therefore determined mainly by the severity of lung hypoplasia and the presence of PPHT causing abnormal pulmonary compliance, refractory respiratory failure at birth, hypoxemia, right to left extrapulmonary shunting of blood, progressive acidosis and heart failure[j] .

CDH is estimated to occur in 1 out of 2,500-5,000 births. There is currently no consensus on the treatment of babies with PPHT. Specific tools in the post-natal treatment of CDH include medical therapies (modern ventilatory strategies, inhaled nitric oxide) and in the absence of response to medical therapy, extracorporeal membrane oxygenation (ECMO). Surgical restoration of abdominal contents to the abdomen is also indicated though the ideal timing of surgery remains undetermined (early vs. delayed; on or off ECMO). Pre-natal laparoscopic intervention for fetal tracheal occlusion has also shown promise. Ultimate respiratory mortality and disability is primarily determined by the physical results of the defect in terms of the absolute number of pulmonary arterioles and their muscular hypertrophy, CDH is often (up to 40% of the time) associated with cardiac, gastrointestinal, genitourinary, skeletal or neural anomalies and with trisomies. Data from the Northern Region Congenital Abnormality Survey database for the period January 1991 to December 2001 confirms that the presence of an additional congenital anomaly was associated with poor survival. Seventy nine (79) percent of neonates with an additional anomaly died. Without an additional anomaly, mortality was 30% ($x^2 = 26.9$; $P < .001$)[k].

Despite the subsequent introduction of advanced medical therapies (e.g., ECMO, iNO, high frequency ventilation, etc., see Table 23 above), survival remains substantially lower for neonates with CDH compared to other causes of PPHN (i.e., Types 1 and 2) and has not improved over the most recent decade[j,k] as identified in Table 25.

Table 25: Effect of New Therapies for PPHN Associated with Congenital Diaphragmatic Hernia

TABLE 1. Effect of New Therapies

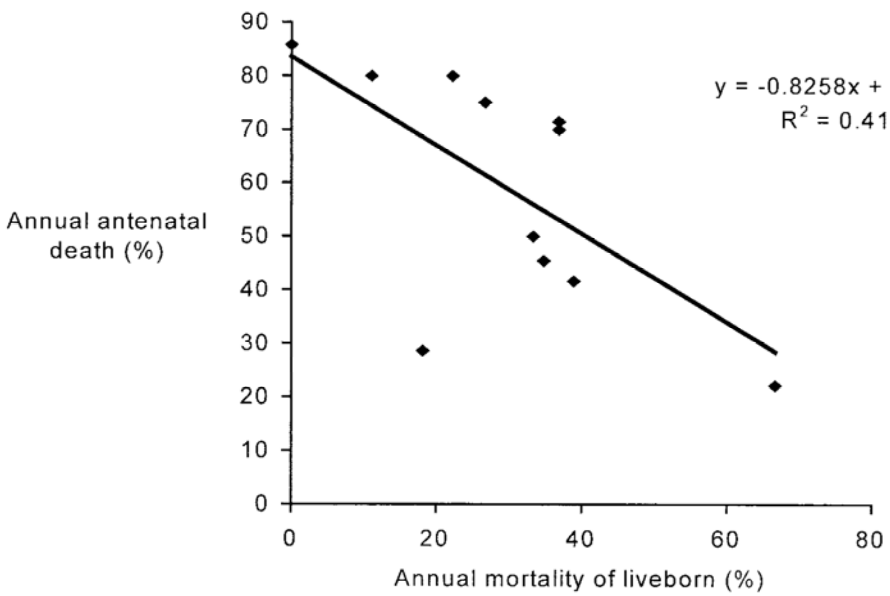
Therapy	Pre-ECMO	ECMO	Post-ECMO	Pre-HFOV	HFOV	Pre-Nitric Oxide	Nitric Oxide	Presurfactant	Surfactant
Total pregnancies	69	73	43	82	103	86	99	124	61
Live births (% antenatal deaths)	51 (26%)	48 (34%)	30 (30%)	63 (23%)	66 (36%)	65 (24%)	64 (35%)	87 (30%)	38 (38%)
No. who received therapy	0	6	0	0	13	0	12	0	9
Survivor	22	31	18	28	43	29	42	45	26
Mortality rate of live births (%)	57	35	40	55	35	55	42	48	38
Overall mortality (%)	68	58	58	65	58	66	57	63	57

j De Buys Roessingh, AS et al. Congenital diaphragmatic hernia: current status and review of the literatureEur J Pediatr (2009) 168:393–406

k Stege G et al. Nihilism in the 1990s: The True Mortality of Congenital Diaphragmatic Hernia. Pediatrics 2003;112:532–535

In addition, when complete ascertainment of all cases is considered by taking into account the hidden mortality of either antenatal termination or postnatal death before transfer to referral centers, further uncertainty is introduced regarding the influence of these advanced therapies on improvements in outcomes for CHD as depicted in Figure 5[k].

Figure 5. Relationship between antenatal death and liveborn infant survival for CDH



Overall, the survival rate is higher in large centers, where a greater number of children are born or transferred every year, than in smaller centers where these cases are few and far between. Unfortunately, the wide disparity in the gravity of CDH presentation prevents valid comparison of treatment results. Despite this, there is wide agreement that even if different types of ventilation, iNO, and ECMO cannot individually be proven to be truly beneficial to babies born with a CDH, their conjunction, or at times their alternance, is beneficial and remain the standard of care[j]. ECMO has become a standard treatment in specialized centers for infants born with a CDH, even though supportive evidence from a randomized trial is lacking. Because ECMO has been associated with neurological complications due to the use of anticoagulant treatment, it is usually reserved for very sick babies with severe pulmonary hypertension and a high risk of hypoxic and ischemic brain injuries. In determining the need for ECMO, the most commonly used calculation is the oxygenation index (OI) calculated by the formula OI= (MAP×FiO2/PaO2), with initiation of ECMO for an OI of 40 or greater[j]. The rule in most centers is to delay reparative surgery until the pulmonary hypertensive crisis in children born with CDH has been controlled, as the repair of a diaphragmatic defect will often worsen pulmonary compliance by reducing the elasticity of the chest wall and increasing the intra-abdominal pressure[j].

Post-Cardiotomy Failure to Wean

ECMO is the most common form of mechanical cardiopulmonary support for children with refractory cardiac failure, with steadily increased use reported over the last 2 decades. Up to 0.5-3.5% of all children undergoing cardiac surgery require mechanical support after repair of congenital heart lesions[l]. ECMO in this setting is used primarily as a bridge to recovery from myocardial stunning. Although rarely needed, it can be life-saving, and remains vital to the management of children with complex congenital cardiac disease[j]. Though the inability to safely provide long-term support or directly vent the left ventricle may prevent optimal results, the timely application of ECMO for post-cardiotomy support can result in improved survival if used appropriately and expeditiously before end-organ injury or cardiac arrest has occurred. Survival rates as high as 60% have been reported for both patients in whom ECMO support was initiated either prior to coming off bypass (failure to wean) and for patients with hemodynamic failure after successful separation from CPB[l]. If prompt recovery leading to ECMO weaning does not occur or is not anticipated, a more permanent cardiac support device or transplantation should be an early consideration.

In a recent study by Chrysostamou et al[m], patients requiring OR ECMO due to failure to wean from CPB had an overall survival rate of 77%, the highest survival to hospital discharge for all cardiac uses in the pediatric population. Chromosomal anomalies, single ventricle anatomy, multiple ECMO runs, high ECMO flows at 24 hours, decreased lung compliance, and plasma exchange were all significant factors associated with mortality. The improved results reported by the authors are attributed to the low incidence of hemodynamically significant residual cardiac defects (3%) and the possibility of lower threshold for placing patients on ECMO.

In 2009, the Extracorporeal Life Support Organization (ELSO) reported that more than 7,500 pediatric patients (3,400 neonates) had been supported with cardiac ECMO since the database began in 1989[n]. During that time, survival to hospital discharge has remained relatively static near 40% and may, in part, be a natural consequence of providing increasingly frequent salvage support to patients with more complex congenital heart disease along with increased use of transition to ECMO during cardiopulmonary

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[l] Jaggers JJ et al. Extracorporeal Membrane Oxygenation for Infant Postcardiotomy Support: Significance of Shunt Management. Ann Thorac Surg 2000;69:1476–83
[m] Chrysostamou, C. et. al. Short- and intermediate-term survival after extracorporeal membrane oxygenation in children with cardiac disease. J Thorac Cardiovasc Surg 2013;146:317-25.)
[n] Haines NM, Rycus PT, Zwischenberger JB, et al. Extracorporeal Life Support Registry Report 2008: neonatal and pediatric cardiaccases. ASAIO J 2009;55:111e16

resuscitation (CPR). Although overall survival for ELSO has been poor for neonates and infants requiring support post cardiac surgery, especially for patients requiring initiation in the ICU and for patients with single ventricle shunt dependent physiologies, reports from isolated centers show excellent results can be obtained in these same situations. Longer duration of extracorporeal membrane oxygenator support, low pH and urine output in the first 24 hours, and renal failure are significant factors associated with mortality during extracorporeal membrane oxygenator support. Exposure to high amounts of blood transfusion during extracorporeal oxygenation, extended extracorporeal membrane oxygenator support, and sepsis increase risk of death after successful decannulation[o]. Dissimilar survival rates amongst numerous reported clinical experiences highlight the difficulties of obtaining reliable comparative data in infant populations with widely disparate etiologies of CHD, completeness of repair, timing of ECMO insertion, and overall clinical condition at the time of ECMO institution. Overall survival to both weaning and discharge is highest for patients with myocarditis and cardiomyopathies (up to 61%)[p].

Since complications rise with time on support, ECMO has generally only been suitable for short-term support, limiting its usefulness as a bridge to transplantation. Furthermore, the size and extracorporeal configuration of the system components usually limit its use to the intensive care unit setting and preclude ambulation and rehabilitation during support. Elective use of the Berlin Heart EXCOR provides better quality support and improved survival for patients in whom transplantation is a likely outcome (bridge to transplant)[q].

Lack of equipoise and Substitute Devices or Therapy

For most of the causes of PPHN (Types 1 and 2), there is strong evidence based on randomized controlled trial (RCT) data supporting ECMO use over standard mechanical ventilation for severe respiratory failure. Fortunately, newer modalities of ventilator management and improved pharmacologic therapy including iNO have resulted in a lower need for ECMO therapy with similar mortality benefit. For clinical situations where available medical therapy has failed and continued reversible cardiopulmonary failure exists, ECMO remains the only viable therapy. Even for these patients, the mortality benefit for ECMO has been clearly and repeatedly demonstrated and approaches 80-90%. **Given the absence of any other available therapy and an imminent outcome of death, equipoise does not exist for a trial of ECMO vs. continued failed therapy in these patients. Similarly, for more complex conditions**

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[o] Kumar TK et al. Extracorporeal membrane oxygenation in postcardiotomy patients: Factors influencing outcome J Thorac Cardiovasc Surg 2010;140:330-6

[p] Rajaghopal SJ et al. Extracorporeal membrane oxygenation for the support of infants, children, and young adults with acute myocarditis: A review of the Extracorporeal Life Support Organization registry. Crit Care Med (2010); 38:382-387

[q] Almond CE et al. Berlin Heart EXCOR Pediatric Ventricular Assist Device for Bridge to Transplant in US Children. *Circulation.* 2013;127:1702-17

and clinical presentations such as CDH and post-cardiotomy support, equipoise does not exist for a randomized trial since the alternative to initiation of therapy for these patients after failure of medical therapy would be death. Although specific pre-manufactured circuits have never been tested for these uses, it should be noted that these clinical results for neonatal and infant ECMO use were achieved in the decade of the 1990s with individual center specific circuits utilizing a variety of off the shelf roller-pumps and older style oxygenators together with uncoated cannulae and tubing circuits designed for short term cardiopulmonary bypass. Improvements in pump, circuit, cannula and oxygenator technology together with standardization of clinical protocols have made ECMO safer overall, though the duration of effective use for these purposes remains limited (7-14 days).

Clinical Conclusion

With clinical utility of ECMO for neonatal and infant cardiopulmonary support in the arena of reversible cardiorespiratory failure, and for failure to wean following cardiac surgery in the pediatric population clearly established, and the benefit/risk profile generally well understood, FDA concludes that there is reasonable assurance of safety and effectiveness of ECMO circuit devices used in these patient populations.

Summary of FDA Recommendation

Mitigations for Identified Risks/Overview of Proposed Special Controls

FDA believes that special controls, in addition to general controls, can be established to mitigate the identified risks and provide reasonable assurance of the safety and effectiveness of ECMO devices where an acute (reversible) condition prevents the patient's own body from providing the physiologic gas exchange needed to sustain life in conditions where imminent death is threatened by respiratory (e.g., meconium aspiration, congenital diaphragmatic hernia, pulmonary hypertension) in neonates and infants, or cardiorespiratory failure (resulting in the inability to separate from cardiopulmonary bypass following cardiac surgery) in pediatric patients. As mentioned previously in the Discussion of Risks to Health Section above, FDA concurs that the risks to health identified by the original classification panel still remain relevant today and has proposed additional risks to health as summarized previously.

The mitigation measures identified below in Table 26 are the result of several years of FDA application review, technological advances, literature reviews, and an expansion of the regulation from a single device to a circuit of devices providing ECMO therapy.

Table 26 Comprehensive List of ECMO Risks and Mitigation Measures

Identified Risk	Recommended Mitigation Measure
Thrombocytopenia	Non-clinical performance evaluation In vivo evaluation Labeling
Hemolysis	Biocompatibility Testing Non-clinical performance evaluation Labeling
Inadequate gas exchange	Non-clinical performance evaluation In vivo evaluation Labeling
Gas embolism	Non-clinical performance evaluation In vivo evaluation Labeling
Mechanical Failure[1]	Non-clinical performance evaluation Labeling
Hemorrhage	In vivo evaluation Labeling
Hemodilution	Non-clinical performance evaluation In vivo evaluation Labeling
Thrombosis/thromboembolism	Non-clinical performance evaluation In vivo evaluation Labeling
Infection	Sterility Shelf life testing
Adverse tissue reaction*	Biocompatibility testing Labeling
Mechanical injury to access vessels	Non-clinical performance evaluation In vivo evaluation Labeling

[1] Mechanical Failure replaces "Loss of Mechanical Integrity" based on comments received on the January 8, 2013 proposed order

* Adverse tissue reaction = Biocompatibility

Based on 1) the fact that ECMO is usually employed in the identified patient population after standard therapies have failed, 2) the history of use of ECMO in the neonatal/infant patient population, and 3) the proposed Special Controls (to include non-clinical performance testing as well as an in vivo evaluation), FDA believes there is sufficient evidence to support renaming and reclassifying 21 CFR 868.5610 Membrane lung for long-term pulmonary support, Class III, to 21 CFR 870.4100 Extracorporeal circuit and accessories for long-term pulmonary/cardiopulmonary support, Class II (Special Controls), in cases where imminent death is threatened by respiratory (e.g., meconium aspiration, congenital diaphragmatic hernia, pulmonary hypertension) in neonates and infants, or cardiorespiratory failure (resulting in the inability to separate from cardiopulmonary bypass following cardiac surgery) in all pediatric patients.

FDA is proposing to modify the regulatory identification/definition for membrane lung for long-term pulmonary support for the following reasons:

- The proposed revisions to the classification regulation, and proposed special controls, take into consideration the unique circumstances surrounding the clinical practice of ECMO. The current regulation is defined very narrowly in terms of both intended use (gas exchange only), and technology (membrane oxygenator only). An ECMO circuit is comprised of individually manufactured and marketed components, and these components are put together by the practicing physician according to indication, patient population and physician preference. A broader definition and identification for this regulation to include the circuit components/accessories (e.g., heat exchanger, cannula, monitors, filters, etc.) needed for long-term extracorporeal support will provide a transparent regulatory pathway for the circuit components to obtain appropriate ECMO labeling, and may provide the best approach to regulate a system (where the circuit components are manufactured and marketed individually) used to provide a therapy.

- The revised regulation is written to include the flexibility needed to regulate future advances in technology, design, and intended use, through the 510(k) regulatory pathway, including significant changes impacting safety and/or effectiveness.

- Indications/conditions where ECMO is not currently considered standard of care, are not identified in the reclassification proposal, as they fall outside the scope of this proposal and are not being considered for reclassification. A new intended use would be subject to the PMA process or granted marketing authority through a *de novo* request.

- The special controls are written to allow for some flexibility in the information necessary to mitigate the risks to health identified for the device. For example, FDA has proposed '*in vivo* evaluation of the device is necessary to demonstrate device performance'. Depending upon the specific device characteristics as well as the available information, *in vivo* evaluation could include clinical data (retrospective and/or prospective, as long as it fits the definition of valid scientific evidence) and/or potentially an animal study to support the performance of critical circuit components.

In summary, when there is an adequate knowledge base and special controls can be established to adequately mitigate the risks to health, a Class II recommendation is appropriate (e.g., ECMO therapy where imminent death is threatened by respiratory (e.g., meconium aspiration, congenital diaphragmatic hernia, pulmonary hypertension) in neonates and infants, or cardiorespiratory failure (resulting in the inability to separate from cardiopulmonary bypass following cardiac surgery) in all pediatric patients.

Regulation

FDA recommends that the current regulation (21 CFR 868.5610) for membrane lung for long-term pulmonary support be ***renamed*** and ***redefined*** to include all circuit components and accessories related to long-term (i.e., >6 hours of use) extracorporeal support. In addition, FDA recommends reclassification of this regulation from Class III to Class II (Special Controls) ***only in conditions where imminent death is threatened by cardiopulmonary failure (e.g., meconium aspiration, congenital diaphragmatic hernia, pulmonary hypertension) in neonates and infants, or cardiorespiratory failure (resulting in the inability to separate from cardiopulmonary bypass following cardiac surgery) in all pediatric patients An acute reversible or treatable cause of respiratory and/or cardiopulmonary failure should be evident, and the subject should demonstrate unresponsiveness to maximum medical or ventilation therapy.***

Current

§ 868.5610 Membrane Lung for Long-Term Pulmonary Support

a) *Identification*: A membrane lung for long-term pulmonary support is a device used to provide to a patient extracorporeal blood oxygenation for longer than 24 hours.

b) *Classification*: Class III (premarket approval).

Proposed

§ 870.4100 *Extracorporeal circuit and accessories for long-term pulmonary/cardiopulmonary support*:

(a) *Identification*. An extracorporeal circuit and accessories for long-term pulmonary/cardiopulmonary support (>6 hours) is a system of devices that provides assisted extracorporeal circulation and physiologic gas exchange of the patient's blood where an acute (reversible) condition prevents the patient's own body from providing the physiologic gas exchange needed to sustain life in conditions where imminent death is threatened by respiratory failure (e.g., meconium aspiration, congenital diaphragmatic hernia, pulmonary hypertension) in neonates and infants, or cardiorespiratory failure (resulting in the inability to separate from cardiopulmonary bypass following cardiac surgery) in all pediatric patients. An acute reversible or treatable cause of respiratory or cardiorespiratory failure should be evident, and the subject should demonstrate unresponsiveness to maximum medical and/or ventilation therapy. The main components of the system include the console (hardware), software and disposables, including, but not limited to, an oxygenator, blood pump, heat exchanger, cannulae, tubing, filters, and other accessories (e.g., monitors, detectors, sensors, connectors).

(b) Class II (special controls). The special controls for this device are:

(i) The design characteristics of the device must ensure that the geometry and design parameters are consistent with the intended use;

(ii) The device(s) must be demonstrated to be biocompatible;

(iii) Sterility and shelf-life testing must demonstrate the sterility of patient-contacting components and the shelf-life of these components;

(iv) Non-clinical performance evaluation of the device must demonstrate substantial equivalence in terms of safety and effectiveness for performance characteristics on the bench, mechanical integrity, EMC (where applicable), software, durability, and reliability, etc.;*

(v) In vivo evaluation of the device must demonstrate device performance over the intended duration of use and for the specific indication; and *

(vi) Labeling must include a detailed summary of the non-clinical and clinical evaluations pertinent to use of the device and adequate instructions with respect to anticoagulation, circuit set up and maintenance during a procedure.

** Additional detail was added to items (iv) and (v) for clarity, as compared to the proposed order published on January 8, 2013.*

If the panel believes that Class II is appropriate for ECMO devices (as defined), the panel will be asked to discuss whether the proposed special controls appropriately mitigate the identified risks to health and/or whether additional or different special controls are recommended.

APPENDIX A

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Appendix B

Publications Included in Literature Review

Meconium Aspiration Syndrome (MAS)

First Author Year	Study Design Population	Sample Size (ECMO)[1]	Gestational Age mean ± SD	Birth Weight (kg)	Duration of Support mean ± SD	Relevant Safety Results
UK Collaborative ECMO Trial (l996, 2001)[2,3]	RCT Infants with severe respiratory failure from 55 hospitals enrolled in a randomized trial, United Kingdom, 1993-1995	ECMO 32 CM 37	Not reported	Not reported	Not reported	*Survival at discharge:* ECMO: 81.25% CM: 56.76% ($p < 0.05$) *Death or Severe Disability at age 4 years* ECMO: 21.9% CM:43% (N.S.)
Graves (1989)[5]	Before/After (Historical Controls) First 28 consecutive ECMO MAS neonates at Ochsner Foundation Hospital (United States) in 1983 compared to MAS neonates prior to the availability of ECMO at the same hospital from 1980 to 1983	ECMO 28 Pre-ECMO 10	Not reported	Not reported	Not reported	*Survival(timeframe not specified):* *ECMO:* 93% Pre-ECMO survival was 30% ($p < 0.001$) *Major causes of death:* Not reported
Extracorporeal Life Support Organization (ELSO)						
Gill (2002)[4]	Case Series ELSO registry 1989-1998 ELSO registry is international Neonates with MAS-induced respiratory failure, treated with ECMO Time from birth to ECMO: ▪ Group 1: 0-23 hours (n=1,266)	3,235	Not reported	Not reported	Not reported	*Survival at discharge*: 94.2% *Survival by group:* Time from birth to ECMO: ▪ 0-23 hours: 95.2% ▪ 24-95 hours: 94% ▪ 96+ hours: 92.3% *Major causes of death:* Not reported

First Author Year	Study Design Population	Sample Size (ECMO)[1]	Gestational Age mean ± SD	Birth Weight (kg)	Duration of Support mean ± SD	Relevant Safety Results
	▪ Group 2: 24-95 hours (n=1,568) ▪ Group 3: 96+ hours (n=401) Limitations: NO or HFOV in one-third of patients					
Radhakrishnan (2007)[7]	Case Series ELSO registry 1989-2004 ELSO registry is international Neonatal patients with respiratory failure from MAS	572	Not reported	Not reported	Not reported	*Survival:* Not reported *Major causes of death:* Not reported *Complications per Patient:* Overall: 1.90 Mechanical: 0.65 ± 0.05 Hematologic: 0.23 ± 0.02 Neurologic: 0.20 ± 0.02 Renal: 0.21 ± 0.02 Pulmonary: 0.13 ± 0.02 Cardiovascular: 0.66 ± 0.03 Infectious: 0.06 ± 0.01 Metabolic: 0.18 ± 0.02
Karimova (2009)[6]	Case series UK Neonatal ECMO Service 1993-2005	345	40 weeks (IQR 38, 41)	3.3 kg (IQR 2.9, 3.7)	100 hours (IQR 78, 138)	*Survival at discharge*: *97.1%*
Young (1997)[8]	Case series ECMO infants at the Children's Hospital of Philadelphia and Children's Hospital in Boston, 1989-1992 Patients followed for ophthalmic complications	35	Not reported	Not reported	Not reported	*Survival:* Not reported *Vasculopathy:* 1/35 (2.86%) (1 Retinal hemorrhage in the L eye)

[1] ECMO or otherwise specified

Abbreviations: CM: Conventional Management; ECMO: Extracorporeal Membrane Oxygenation; ELSO: Extracorporeal Life Support Organization; HFOV: High Frequency Oscillatory Ventilation; MAS: Meconium Aspiration Syndrome; NO: Nitric Oxide; N.S.: Not Statistically Significant ($p>0.05$); RCT: Randomized Clinical Trial; UK: United Kingdom; VA: Veno-arterial.

Congenital Diaphragmatic Hernia (CDH)

First Author Year	Study Design Population	Sample Size (ECMO)[1]	Gestational Age mean ± SD[1]	Birth Weight (kg)[1]	Duration of Support mean ± SD[1]	Relevant Safety Results[1]
Morini (2006)[18]	Meta-analysis Early mortality studies (before discharge): 19 observational studies Late mortality studies (after discharge): 8 observational studies RCT (ECMO vs. CMV): 2 studies	ECMO Early: 1,084 Late: 726 No ECMO Early:406 Late: 368	Not reported	Not reported	Not reported	RCTs *Survival* Before discharge on ECMO: 35% Before discharge CMV: 10.5% (p<0.05) After discharge on ECMO: 25% After discharge CMV: 5% (N.S) Retrospective Studies *Survival* Before discharge on ECMO: 65.5% Before discharge no ECMO: 46.8% (p < 0.001) After discharge on ECMO: 64.5% After discharge no ECMO: 43.4% (p < 0.001)
UK Collaborative ECMO Tria (l996, 2001)[2,3]	RCT Infants with severe respiratory failure from 55 hospitals enrolled in a randomized trial, 1993-1995	ECMO 18 CM 17	Not reported	Not reported	Not reported	*Survival:* CDH ECMO: 4/18 (22.22%) CDH CM: 0/17 (0%) (p = 0.10) *Death or Severe Disability at age 4 years* ECMO: 89% CM: 100% (N.S.)
The Congenital Diaphragmatic Hernia Study Group (CDHSG) (2009)[11]	Cross-sectional CDHSG registry 1995-2005 CDHSG registry is international Patients who underwent CDH repair during or after ECMO therapy	636	Not reported	3.11 ± .052	10.6 ± 6.1 days	*Survival to discharge:* 60.6% ▪ Repaired on ECMO: 48.2% ▪ Repaired after ECMO: 77.1% (p < .01) *Major causes of death:* Not reported *Other:*

First Author Year	Study Design Population	Sample Size (ECMO)[1]	Gestational Age mean ± SD[1]	Birth Weight (kg)[1]	Duration of Support mean ± SD[1]	Relevant Safety Results[1]
	CDH Side: Right: 22.4% Limitations: 1) Excludes very severe cases (patients died before repair) 2) Excludes patients repaired before ECMO					Required supplemental oxygen at discharge: 52.4% Required tube feeds at discharge: 47.9%
Hanekamp (2003)[15]	Cross-sectional CDH patients admitted to the pediatric surgical ICU at Erasmus MC-Sophia (Netherlands), 1990-2001 CDH repair and ECMO (n=24) Female: 37.5% Male: 62.5% CDH repair without ECMO Female: 41.5% Male: 58.5%	ECMO 24 Without ECMO 65	39 +1 weeks 38 +5 weeks	3.087 3.095	Not reported	*Survival:* Not reported *Major causes of death:* Not reported *Other:* 21% developed a chylothorax (accumulation of chyle in the thoracic cavity) vs. 6% in CDH patients without ECMO ($p < .05$) Authors conclude that chylothorax *“should be considered the result of the severity of the defect rather than the consequence of ECMO”* and *“ECMO is more likely to be a selection bias for the development of a CT than the cause of the CT”*
Extracorporeal Life Support Organization (ELSO)						
Dimmitt (2001)[12]	Case Series ELSO registry 1990-1999 ELSO registry is international Infants with CDH treated with VA ECMO 43.8% Female 56.2% Male	2,257	38.7 ± 2 weeks	3.1 ± 0.6	9.6 ± 5.7 days	*Survival to discharge:* 52.2% *Major causes of death:* Not reported *CNS complications:* Brain death: 1.2% Seizures: 12.3%

First Author Year	Study Design Population	Sample Size (ECMO)[1]	Gestational Age mean ± SD[1]	Birth Weight (kg)[1]	Duration of Support mean ± SD[1]	Relevant Safety Results[1]
	CDH Side: ▪ Left: 68% ▪ Right:18.2% ▪ Unspecified:13.8% ▪ Bilateral:0.04%					Infarct: 10.5% Hemorrhage: 5.8% *Renal complications:* Renal dialysis: 3.6% Hemofiltration: 16% SCUF: 2.1% CAVHD: 8% *Cardiopulmonary complications:* Cardiac stun: 13.1% Pneumothorax: 8.5% Pulmonary hemorrhage: 8% Arrhythmia: 7.2% Pressors: 6.6% *Other:* DIC: 0.6%
Ryan (1994)[19]	Case Series ELSO registry 1973-1992 ELSO registry is international 17 infants with CDH and *congenital heart disease* receiving ECMO in the U.S. or Canada Limitation: Of 17 infants, 1 had VV ECMO and 1 had both VA and VV ECMO; the results reported here are not specific to VA patients	17	39 (35-43) weeks	2.8 (2-3.4)	198 (59-360) hours	*Survival:* 29.4% *Major causes of death:* Not reported *Complications:* Surgical bleeding (n = 5) Intracranial hemorrhage (n = 2) Seizures (n = 2) Arrhythmias (n = 2) Acidosis (n = 2)
Dyamenahalli (2013)[13]	Case Series ELSO registry 1998-2010 ELSO registry is international Infants with CDH and *congenital heart disease*	316	38 (29-42)* weeks *median	3 (1.35-4.7)* *median	194 (3-823) hours* *median	*Survival to discharge* 47% *Major causes of death:* Not reported

First Author Year	Study Design Population	Sample Size (ECMO)[1]	Gestational Age mean ± SD[1]	Birth Weight (kg)[1]	Duration of Support mean ± SD[1]	Relevant Safety Results[1]
	receiving ECMO Limitation: >90% of infants placed on VA ECMO; results reported here are not specific to VA patients					
Aly (2010)[9]	Case Series National Inpatient Sample and 'Kids' database 1997-2004 All-payer database, ~1,000 hospitals in 37 states Infants with CDH treated with ECMO, inborn only	171	Age at admission <8 days	Not reported	Not reported	*Survival:* Survived to surgery: 80.7% Survival in operated patients: 57.3% *Major causes of death:* Not reported
Karimova (2009)[6]	Case Series UK Neonatal ECMO Service 1993-2005	141	40 weeks (IQR 38, 41)	*Median* 3.3 kg (IQR 2.9, 3.7)	196 hours (IQR 120, 341)	*Survival at discharge*: 57.9%
Grist (2010)[14]	Case Series CDH patients treated with ECMO, Kansas City, MO, 1989-2008	93	Age: (0-12) days	Not reported	(3-662) hours	*Survival:* Survival to discharge: 55% Survival if: Surgery before ECMO: 85% ECMO before Surgery: 67% Surgery while on ECMO: 28% ECMO but no Surgery: 0% Late or no Surgery (combination): 43%
Kugelman (2003)[17]	Case Series Study comparing VV and VA ECMO in newborns with CDH at Huntington Memorial Hospital (Pasadena, CA), 1990-2001	46 VA: 19 VV: 27	VA: 36.9 ± 0.3 weeks VV: 39.0 ± 0.3 weeks	VA: 2.77 ± 0.11 VV: 3.34 ± 0.11	VA: 150.3 ± 22.1 hours VV: 152.0 ± 14.9 hours	*Survival:* VA: 68% VV: 69% (ns)

First Author Year	Study Design Population	Sample Size (ECMO)[1]	Gestational Age mean ± SD[1]	Birth Weight (kg)[1]	Duration of Support mean ± SD[1]	Relevant Safety Results[1]
	Male: VA: 63%; VV: 54% CDH repair before ECMO: VA: 10.5%; VV: 19% Surgery during ECMO: VA: 89.5%; VV: 69% Mechanical ventilation (days): VA: 33.5 ± 5.5; VV: 32.0 ± 5.6 (ns)		($p < 0.05$)	($p < 0.05$)	(N.S)	*Major causes of death:* Not reported *Other:* Head ultrasound/CT scan: VA: 10.5% VV: 3.8% (N.S) Myocardial stun: VA: 15.8% VV: 3.8% (N.S)
Jaillard (2003)[16]	Case Series Infants with CDH admitted to NICU, University Teaching Hospital at Lille, France, 1991-1998 Limitations: 18% VV ECMO; reported results not specific to VA patients	26	Not reported	Not reported	7 (5 to 14) days* *Median	*Survival at 2 years:* 69% *Major causes of death:* Not reported Outcomes at 2 Years (n = 18): *Neurological Outcomes:* Cerebral palsy: 6% Developmental delay: 17% *Nutritional Outcomes:* Growth retardation: 44% Gastroesophageal reflux: 50% Nutritional Support: 11% *Respiratory Outcomes:* Chronic lung disease: 56% Needing tracheostomy: 5.5% Oxygen requirement: 5.5% *Other:* Scoliosis: 11% Recovery without sequelae: 22%
Antunes (1995)[10]	Case Series	18	Not reported	Not reported	Not reported	*Survival to discharge:* 44%

First Author Year	Study Design Population	Sample Size (ECMO)[1]	Gestational Age mean ± SD[1]	Birth Weight (kg)[1]	Duration of Support mean ± SD[1]	Relevant Safety Results[1]
	Infants with unrepaired CDH admitted to Thomas Jefferson University Hospital, 1991-1994 18 infants required VA ECMO after progressive respiratory failure *that did not respond to high-frequency ventilation*					*Major causes of death:* Not reported

[1] ECMO or otherwise specified

Abbreviations: CAVHD: Continuous Arteriovenous Hemodialysis; CDH: Congenital Diaphragmatic Hernia; CDHSG: The Congenital Diaphragmatic Hernia Study Group; CM: Conventional Management; CMV: Conventional Mechanical Ventilation; CNS: Central Nervous System; CT: Chylothorax; DIC: Disseminated Intravascular Coagulation; ECMO: Extracorporeal Membrane Oxygenation; ELSO: Extracorporeal Life Support Organization; ICU: Intensive Care Unit; IQR: Interquartile Range; NICU: Neonatal Intensive Care Unit; N.S.: Not Statistically Significant (p>0.05); RCT: Randomized Clinical Trial; SCUF: Slow Continuous Ultrafiltration; UK: United Kingdom; VA: Veno-arterial ; VV: Veno-venous.

Primary Persistent Pulmonary Hypertension of the Neonate (PPHN)

First Author Year	Study Design Population	Sample Size (ECMO)[1]	Gestational Age mean ± SD (range)[1]	Birth Weight (kg)[1]	Duration of Support mean ± SD (range)[1]	Relevant Safety Results[1]
Lazar (2012)[20]	Case Series ELSO Registry 2000-2010 ELSO registry is international	ECMO: 1,569 patients ECMO: 3,422 complications	38.7 ± 0.2 weeks	Not reported	6.8 ± 0.1 days	*Survival to discharge* *Overall Survival: 81%* *By time in ECMO support:* • *7 days: 88%* • *10 days: 78%* • *14 days: 55%* • *21 days: 25%* *Major Causes of Death:* ▪ *Lung Recovery: 49%* ▪ *Organ Failure: 21%* ▪ *Hemorrhage: 12%* ▪ *Incompatible with life: 12%* ▪ *Family Request: 6%* ▪ *Unknown: 1%* *Complications* - *74% neonates* *Distribution of Complications* ▪ *Cardiovascular: 32%* ▪ *Mechanical: 26%* ▪ *Renal: 11%* ▪ *Metabolic: 9%* ▪ *Hemorrhagic: 8%* ▪ *Neurologic: 8%* ▪ *Pulmonary: 4%* ▪ *Infectious: 2%* *Complications per patient:* *Overall: 2.2* *By ECMO duration* • *4-7 days: 1.79* • *8-10 days: 2.31* • *11-14 days: 3.19* • *>14 days: 4.17*

First Author Year	Study Design Population	Sample Size (ECMO)[1]	Gestational Age mean ± SD (range)[1]	Birth Weight (kg)[1]	Duration of Support mean ± SD (range)[1]	Relevant Safety Results[1]
Karimova (2009)[6]	Case Series UK Neonatal ECMO Service 1993-2005	68	40 weeks (IQR 38, 41)	3.3 kg (IQR 2.9, 3.7)	115 hours (IQR 84,149)	*Survival at discharge*: *79.4%*
Young (1997)[8]	Case series ECMO infants at the Children's Hospital of Philadelphia and Children's Hospital in Boston, 1989-1992 Patients followed for ophthalmic complications	19	Not reported	Not reported	Not reported	*Survival:* *Not reported* *Vasculopathy:* *0/19 (0%)*

[1] ECMO or otherwise specified

Abbreviations: ECMO: Extracorporeal Membrane Oxygenation; ELSO: Extracorporeal Life Support Organization; IQR: Interquartile Range; PPHN: Primary Persistent Pulmonary Hypertension of the Neonate; UK: United Kingdom.

Infant Failure to Wean (FTW)

First Author Year	Study Design Population	Sample Size (ECMO)[1]	Gestational Age mean ± SD (range)[1]	Birth Weight (kg)[1]	Duration of Support mean ± SD (range)[1]	Relevant Safety Results[1]
Sherwin (2012)[23]	Case Series ELSO Registry 2000-2009 ELSO registry is international Infants with HLHS (congenital heart disease) and placed on ECMO after failure to wean from CPB.	209	Not reported	Not reported	Not reported	Survival: 34%
Bhat (2013)[21]	Case Series Infants weighing 3 kg or less and placed on ECMO after failure to wean from CPB, Mott Children's Hospital (Michigan, USA), 1999-2010	39	Not reported	Not reported	Not reported	*Survival at 30 days:* 67%
Hamrick (2003)[22]	Case Series Infants with congenital heart disease supported postoperatively with ECMO d/t failure to wean from CPB, California, 1990-2001	21	Not reported	Not reported	Not reported	*Survival*: 38%

[1] ECMO or otherwise specified.

Abbreviations: CPB: Cardiopulmonary Bypass; ECMO: Extracorporeal Membrane Oxygenation; ELSO: Extracorporeal Life Support Organization; FTW: Failure to Wean; HLHS; hypoplastic left heart syndrome.

Adult Failure to Wean (FTW)

First Author Year	Study Design Population	Sample Size (ECMO)[1]	Age mean ± SD[1]	BMI[1]	Duration of Support mean ± SD[1]	Relevant Safety Results[1]
Hsu (2010)[25]	Case Series Cardiac surgery patients unable to wean from CPB and experiencing postcardiotomy cardiogenic shock, Taiwan, 2002-2006 Female: 29% Male: 71%	51	63 ± 15.7 years	21.5 ± 4.1	7.5 ± 6.7 days	*Survival:* Hospital survival: 33% 30-Day survival: 51% 1-Year survival: 29% *Major causes of death:* Pulmonary infections *Complications:* Acute renal failure: 75% Femoral bleeding: 39% Haematuria: 33% GI bleeding: 25% Pulmonary infection: 22% Compartment syndrome: 9.8% ARDS: 9.8% Limb ischaemia: 5.9% Leg amputation: 3.9% Neurologic complications: 5.9% Catheter-related infection: 5.9% Pancreatitis: 2.0%
D'Alessandro (2011)[24]	Case Series Isolated cardiac transplant patients unable to wean from CPB, France, 2003-2008	48	Not reported	Not reported	Not reported	*Survival:* 1-year survival: 33.33% *Major causes of death:* Not reported
Muehrcke (1995)[26]	Case Series The Cleveland Clinic 1992-1994	15	Not reported	Not reported	Not reported	*Survival to discharge* 47% *Major causes of death:* Cardiac: 50% (4/8) Multiple organ failure: 50% (4/8)

[1] ECMO or otherwise specified.
Abbreviations: ARDS: Acute Respiratory Distress Syndrome; CPB: Cardiopulmonary Bypass; ECMO: Extracorporeal Membrane Oxygenation; FTW: Failure to Wean; GI: Gastrointestinal.